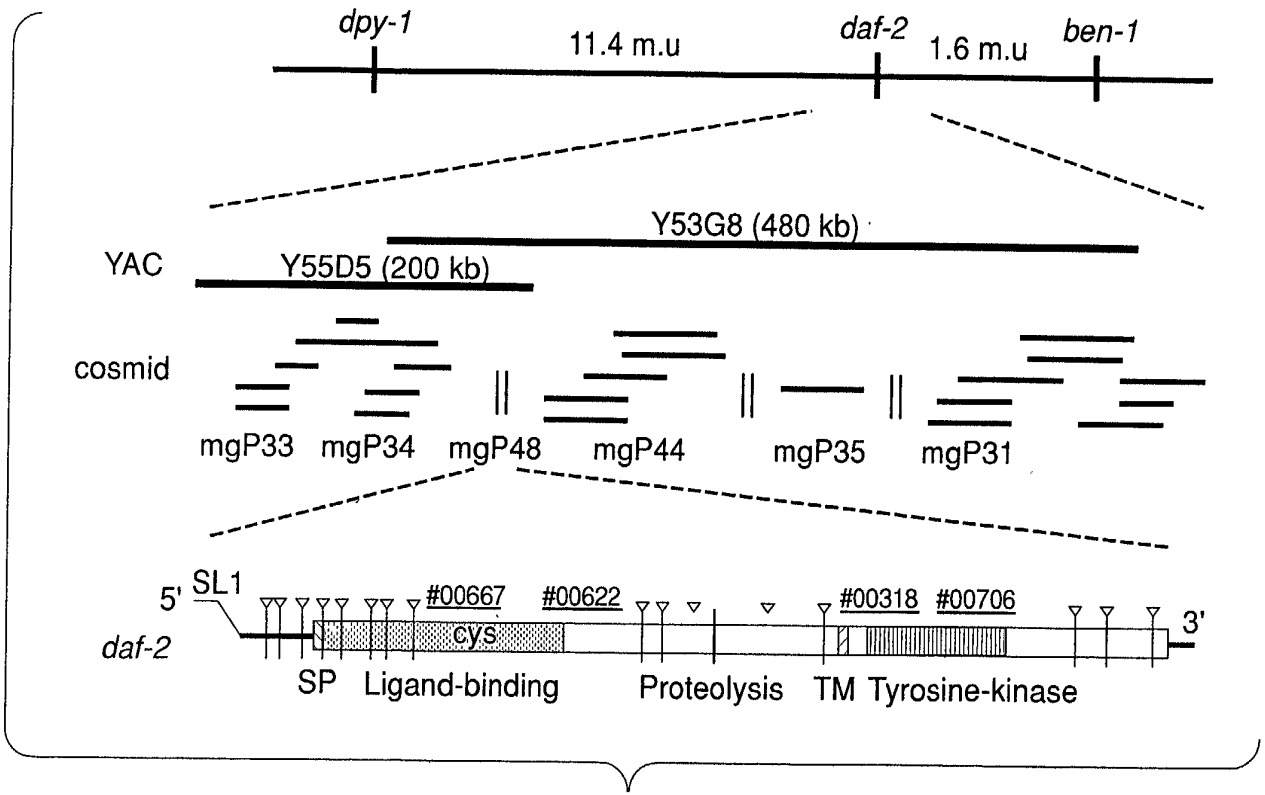

Fig. 1

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 301 IEKCDAHLYLLLQRRCVTREQCLQLNPVLSNKTVPIKATAGLCSDKCPDGYQINPDDHRE
 361 CRKCVGKCEIVCEINHVIDTFPKAQAIRLCNIIDGNLTIEIRGKQDSGMASELKDIFANI
 421 HTITGYLLVRQSSPFISLNMFRNLRRIEAKSLFRNLYAITVFENPNLKKLFDSTTDLTLD
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 541 VFFSWPSFNITDIDQRKFLGYELFFKEVPRIDENMTIEEDRSACVDSWQSVFKQYYETSN
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Fig. 2A

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Fig. 2B (sheet 1 of 3)

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Fig. 2B (sheet 2 of 3)

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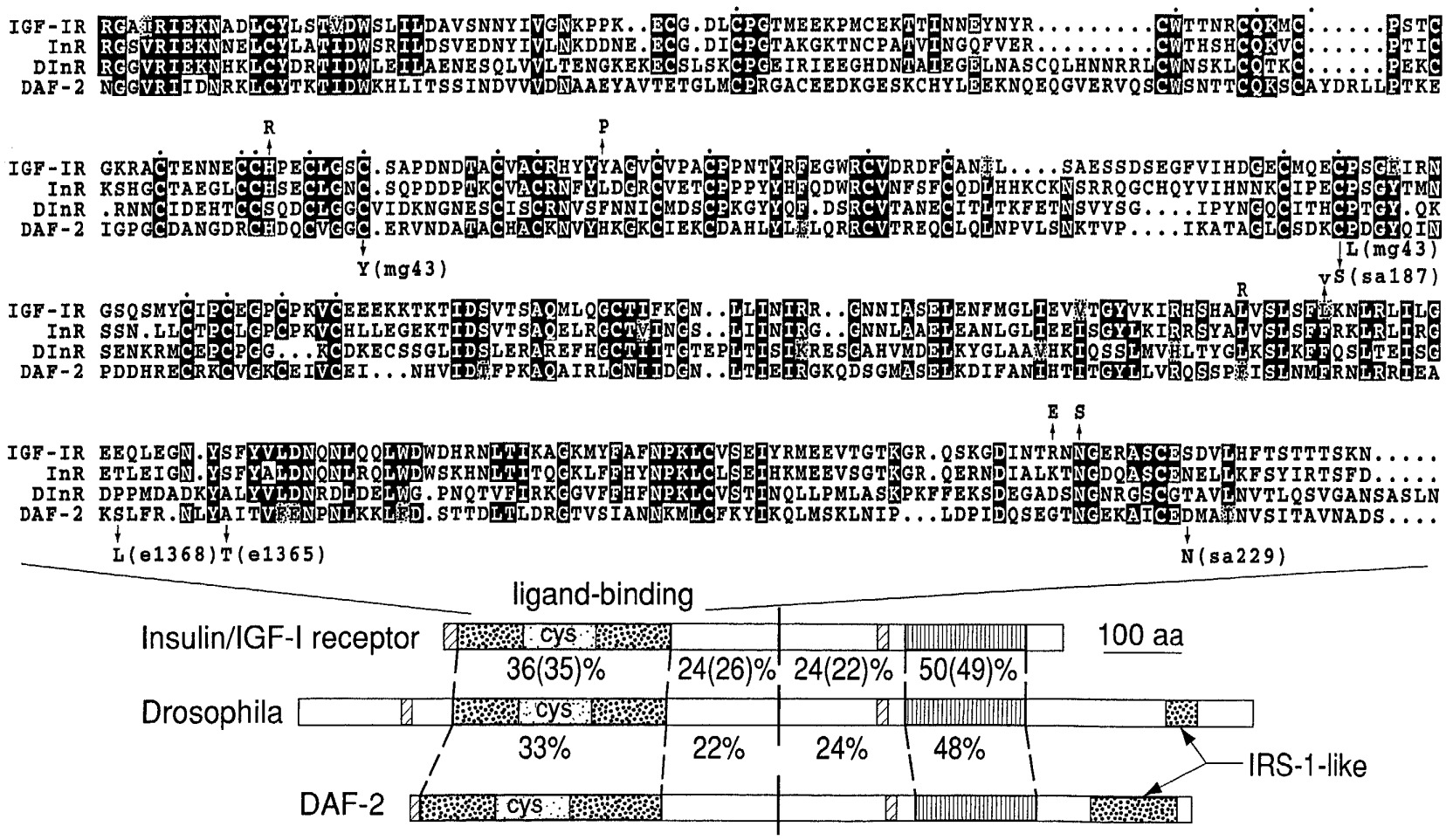
Fig. 2B (sheet 3 of 3)



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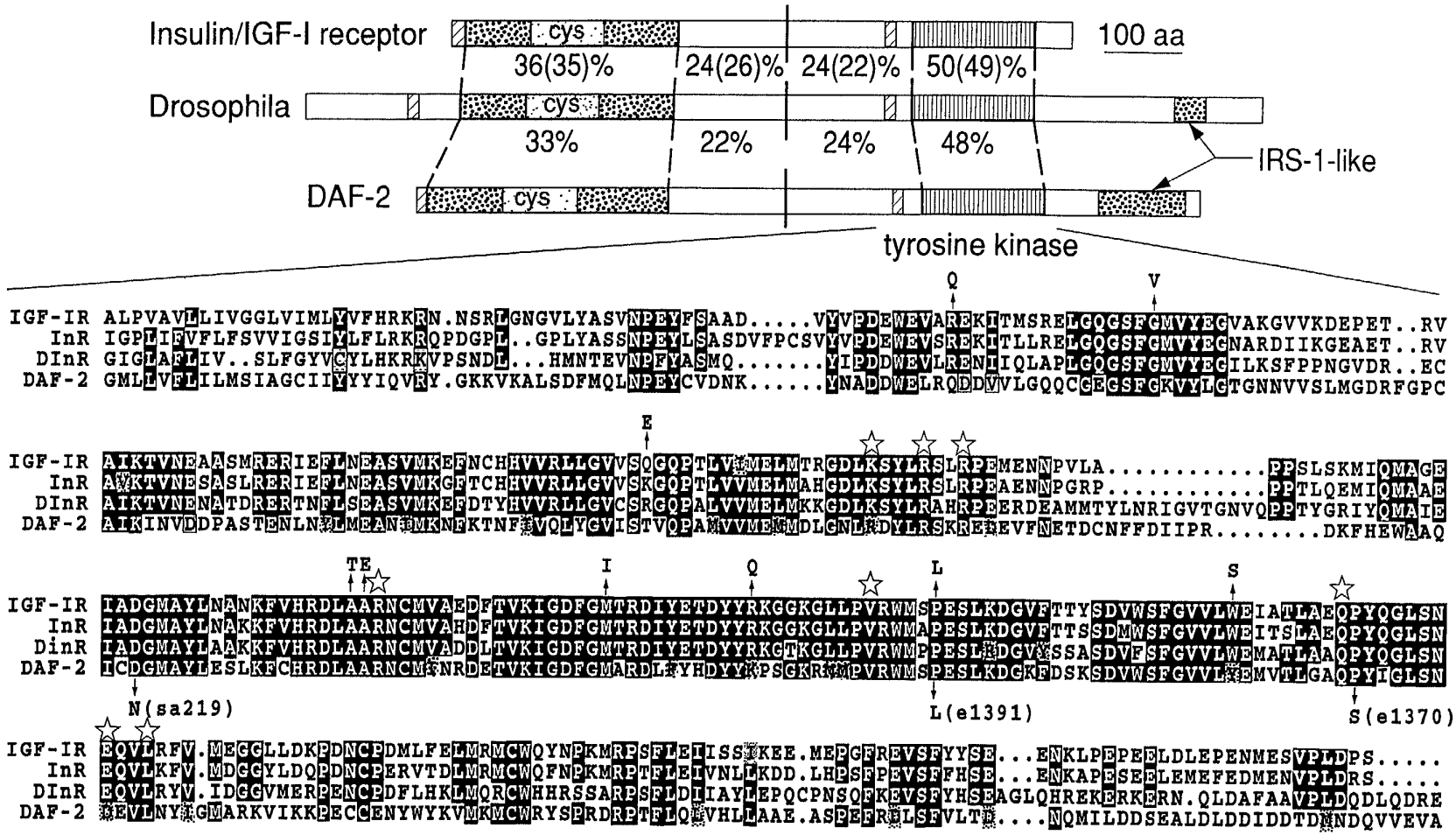


Fig. 2C (sheet 2 of 2)

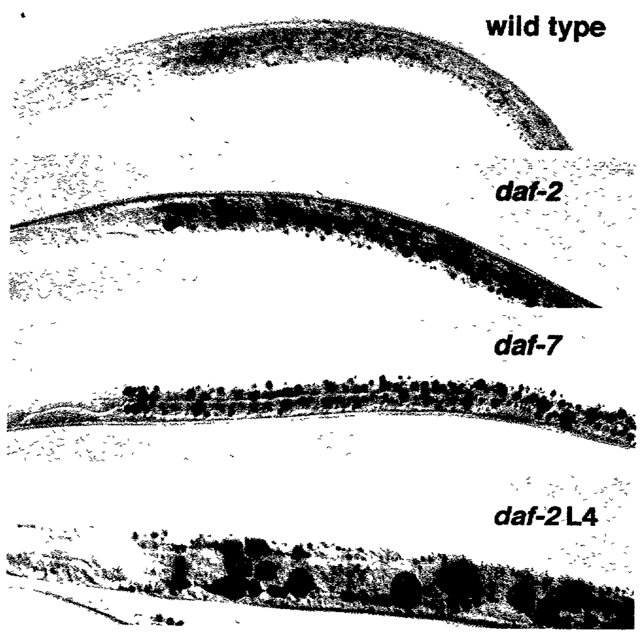
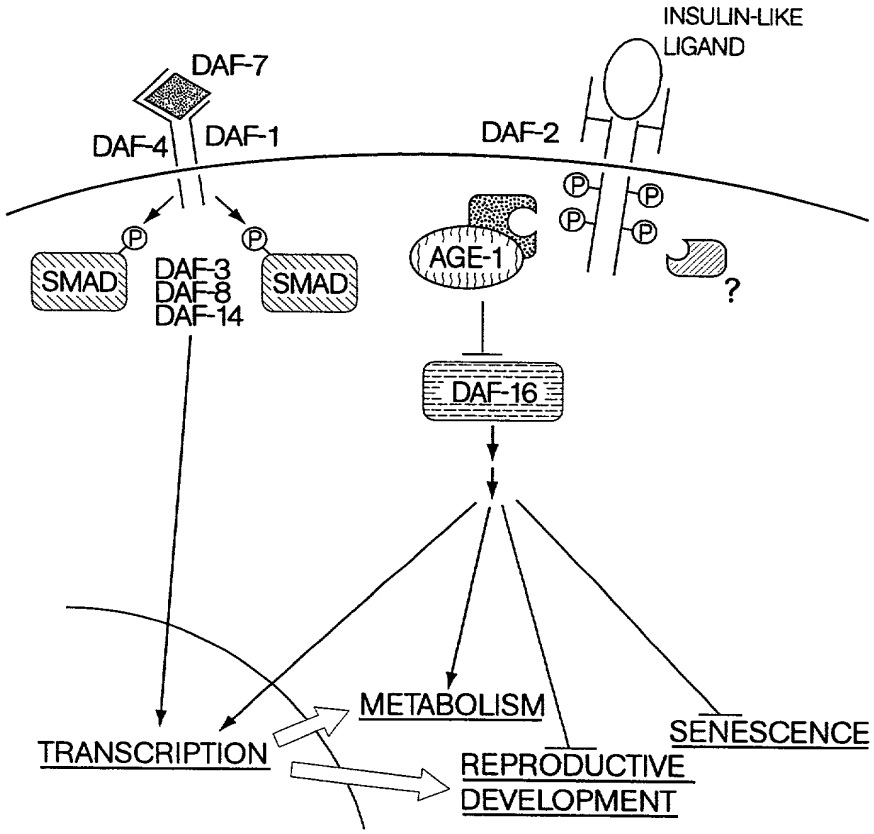


Fig. 3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DAF-4
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?
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TRANSCRIPTION
METABOLISM
SENESCENCE
REPRODUCTIVE
DEVELOPMENT

Fig. 4

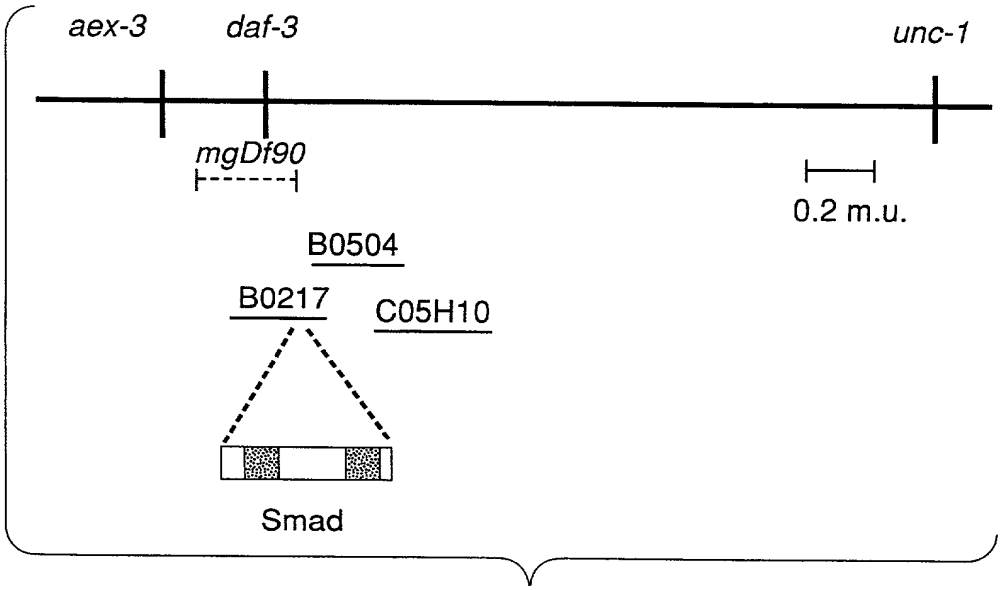
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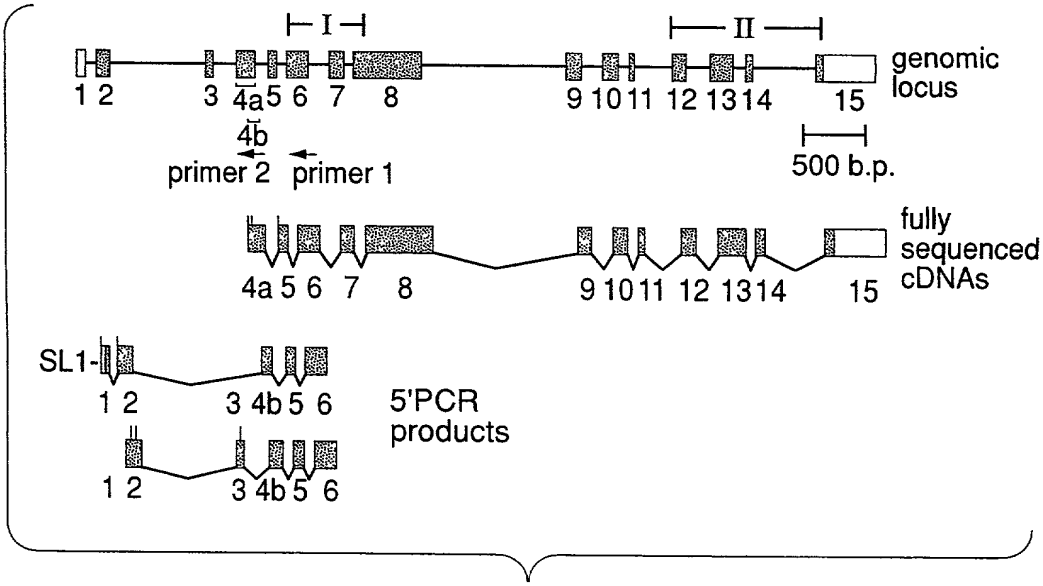
Fig. 5A


I
II
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4b
primer 2
primer 1
500 b.p.
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9 10 11 12 13 14 15
fully sequenced cDNAs
SL1-
1 2 3 4b 5 6
5'PCR products
1 2 3 4b 5 6

Fig. 5B

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Domain I

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DPC4    GGESETFAKRAIESLVKKLKEKKDELDSLITAITTNGAHPSKCVTIQRTLDG
            mg125 P->L
        RLQVHGRKGFPHVVYGKLWRFNEMTKNETRHVDHCKHAFEMKSDMVCVNPYH
        |||| |||||||| |  |||     |||  ||  |  ||  | | |||||||
        RLQVAGRKGFPHVIYARLWRWPDLHKNELKHVKYCQYAFDLKCDSVCVNPYH


Domain II

DAF-3   IVYYEKNLQIGE..KKCSRGNFHVDGGFI..CSENRYSLGLEPNPIREPVAFKV
        | | |   | ||  |  |        |        |  ||   |  |
DPC4    IAYFEMDVQVGETFKVPSSCPIVTVDGYVDPSGGDRFCLGQLSNVHRTEAIERA
       mg132  G->E
        RKAIVDGIRFSYKKDGSVWLQNRMKYPVFVTSGYLDEQSGGLKKDKVHKVYGCA
        |  |  |     |  | ||        ||| | |||   |    | ||| |  |
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Fig. 5C

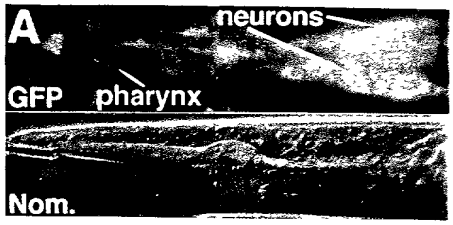


Fig. 6A

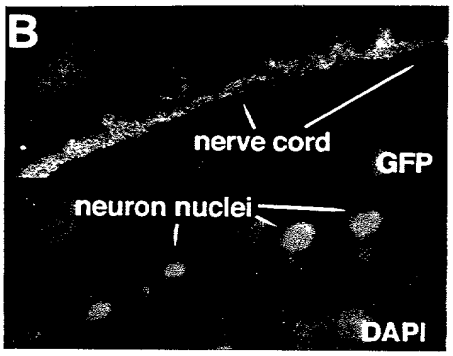


Fig. 6B

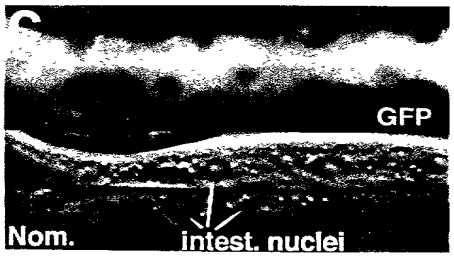
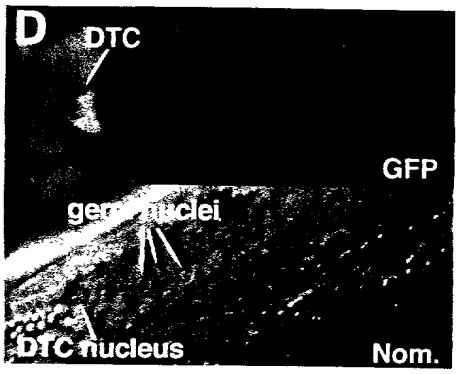


Fig. 6C



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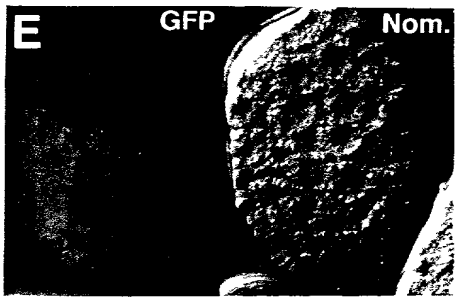


Fig. 6E

Fig. 6F

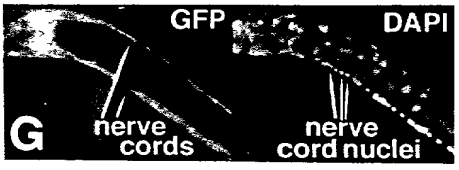


Fig. 6G

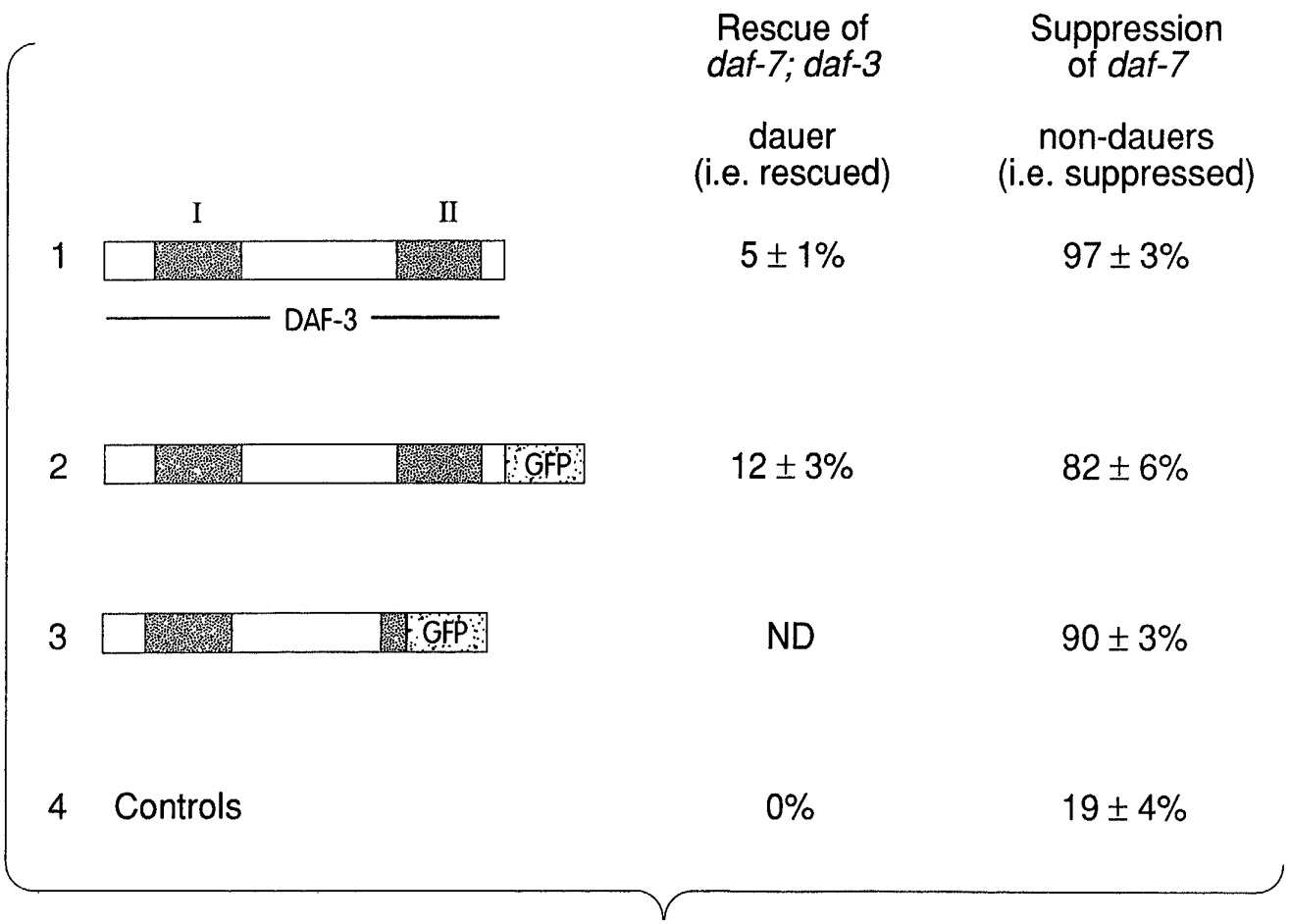
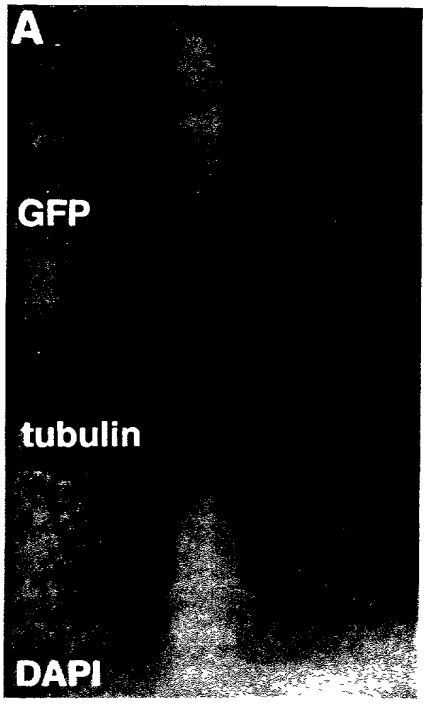


Fig. 7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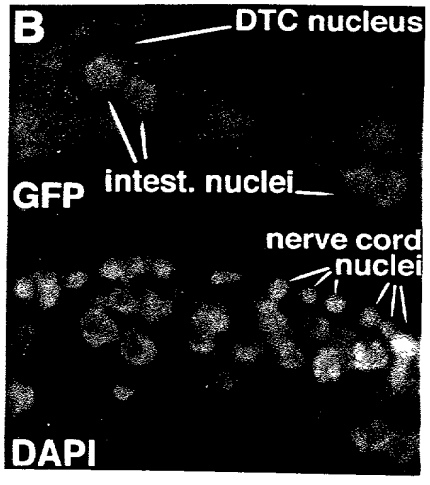
GFP
tubulin
DAPI

Fig. 8A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DTC nucleus
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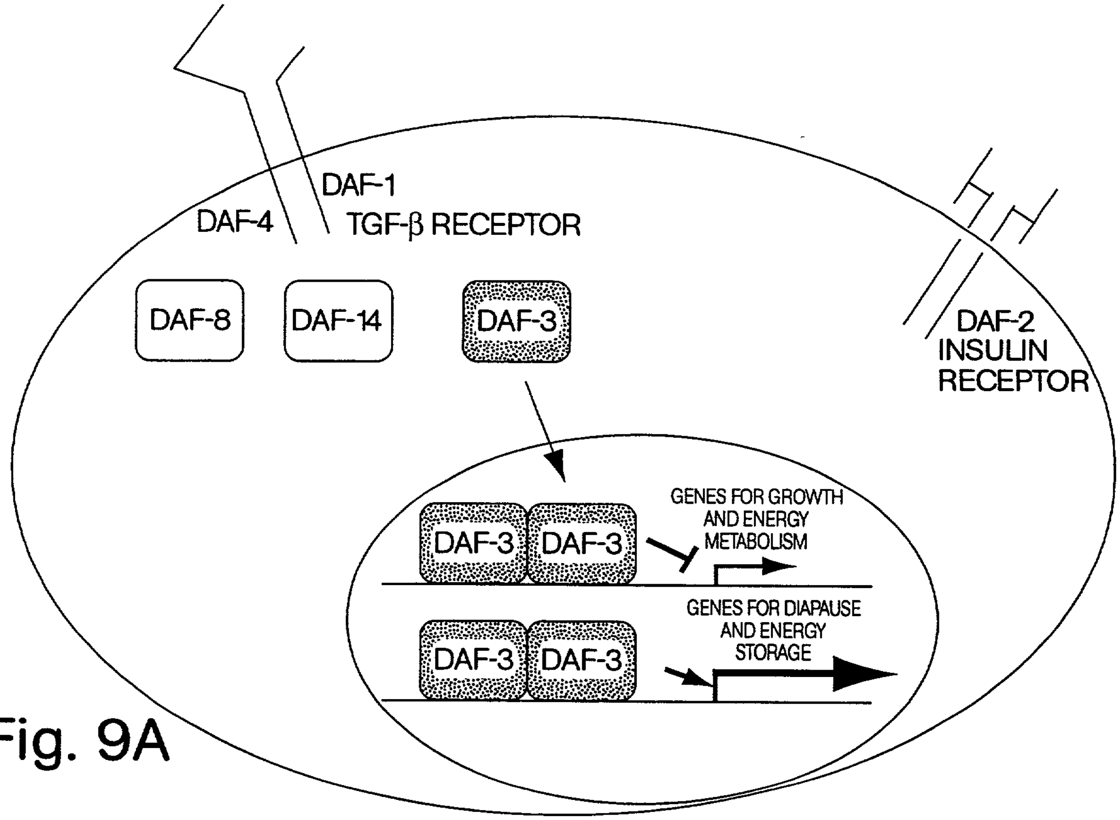
GFP
nerve cord
nuclei
DAPI

Fig. 8B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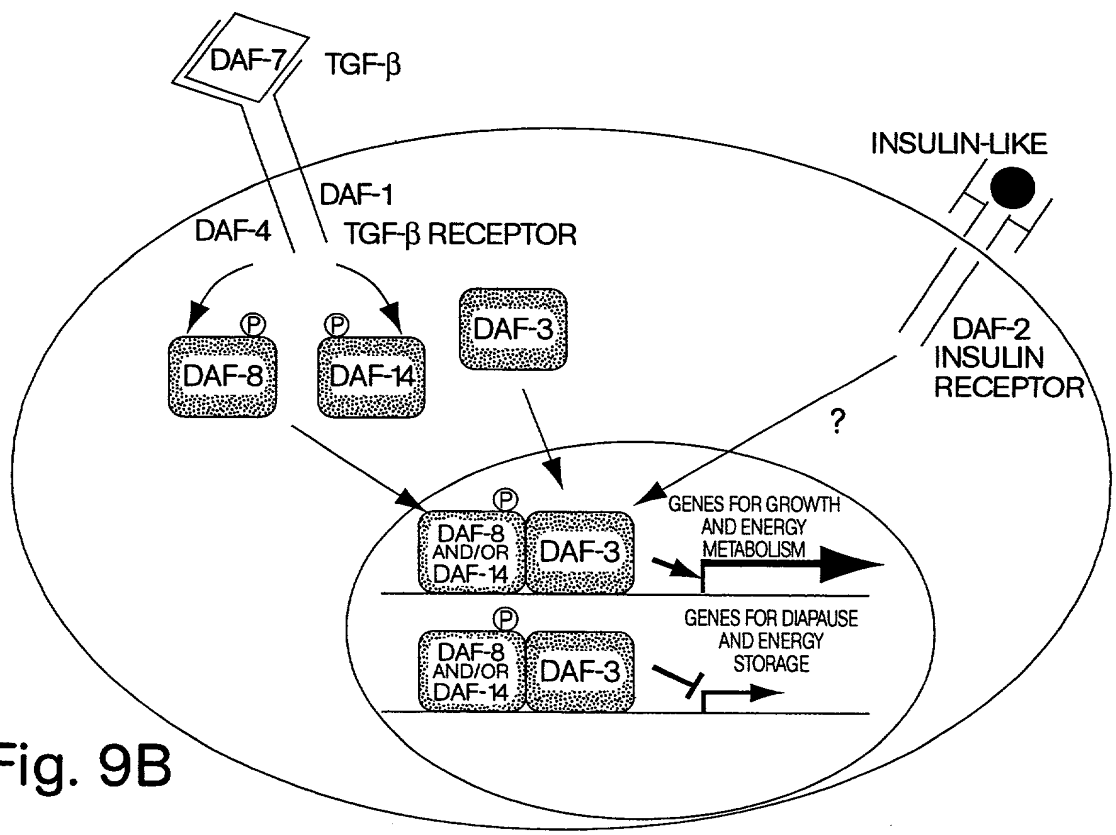
DAF-4
TGF-β RECEPTOR
DAF-8
DAF-14
DAF-3
DAF-2
INSULIN
RECEPTOR
DAF-3
DAF-3
GENES FOR GROWTH
AND ENERGY
METABOLISM
DAF-3
DAF-3
GENES FOR DIAPAUSE
AND ENERGY
STORAGE

Fig. 9A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TGF-β
INSULIN-LIKE
DAF-1
DAF-4
TGF-β RECEPTOR
P
DAF-8
P
DAF-14
DAF-3
DAF-2
INSULIN
RECEPTOR
?
P
DAF-8
AND/OR
DAF-14
DAF-3
GENES FOR GROWTH
AND ENERGY
METABOLISM
P
DAF-8
AND/OR
DAF-14
DAF-3
GENES FOR DIAPAUSE
AND ENERGY
STORAGE

Fig. 9B

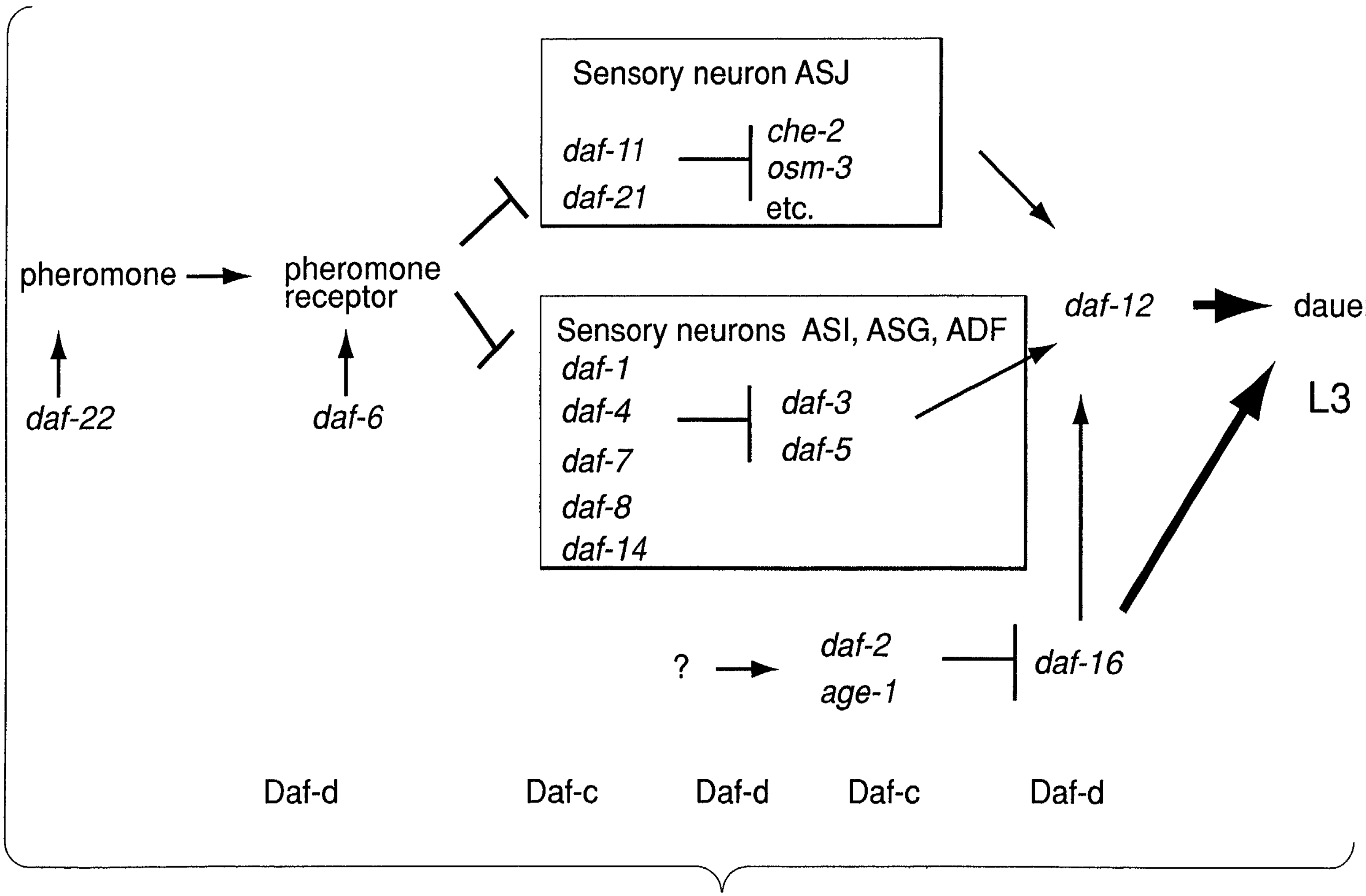

Fig. 10

1 atgaagctaa tagcaacttc tcttctagtt cccgacgagc acacaccgat
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101 aaatggaaat cccgccatat ttggatccag acagtcagga tgatgacccg
151 gaagatggtg tcaactaccc ggatccagat ttatttgaca caaaaaacac
201 aaatatgacc gagtacgatt tggatgtgtt gaagcttgga aaaccagcag
251 tagatgaagc acggaaaaag atcgaagttc ccgacgctag tgcgccgcca
301 aacaaaattg tagaatattt gatgtattat agaacgttaa aagaaagtga
351 actcatacaa ctgaatgcgt atcggacaaa acgaaatcga ttatcgttga
401 acttggtcaa aaacaatatt gatcgagagt tcgaccaaaa agcttgcgag
451 tccctggtga aaaaattgaa ggataagaag aatgatctcc agaacctgat
501 tgatgtggtt ctttcaaaag gtacaaaata taccggttgc attacaattc
551 caaggacact tgatggccgg ttacaggtcc acggaagaaa aggtttccct
601 cacgtagtct atggcaaact gtggaggttt aatgaaatga caaaaaacga
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701 tggtatgcgt gaatccctat cactacgaaa ttgtcattgg aactatgatt
751 gttgggcaga gggatcatga caatcgagat atgccgccgc cacatcaacg
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1201 aacttgtacg ggtttccaac tccttatccg gattttcacc atcctttcaa
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2001 gtctatcaaa acgtttggct tcaacgtttc caaacaaatc atcagagacg
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Fig. 11A (sheet 1 of 2)

```
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2151  agcaacacgc accactgatt cattggccaa gtactgttgt gtccgtgtct
2201  cgttctgcaa aggatttgga gaagcatacc cagaacgccc gtcaattcat
2251  gattgtccag tttggattga gttgaaaatc aacattgcct acgatttcat
2301  ggattcaatc tgccagtaca taaccaactg cttcgagccg ctaggaatgg
2351  aagattttgc aaaattggga atcaacgtca gtgatgacta aatgataact
2401  tttttcactc accctactag atactgattt agtcttattc caaatcatcc
2451  aacgatatca aacttttcc tttgaacttt gcatactatg ttatcacaag
2501  ttccaagcag tttcaataca aacataggat atgttaacaa cttttgataa
2551  gaatcaagtt accaactgtt cattgtgagc tttgagctgt atagaaggac
2601  aatgtatccc atacctcaat ctttaatagt catcagtcac tggtcccgca
2651  ccaatttttt cgattcgcat atgtcatata ttgcaccgtg gccctttta
2701  ttgtaacttt taatatattt tcttcccaac ttgtgaatat gattgatgaa
2751  ccaccatttt gagtaataaa tgtatttttt gtgg
```

Fig. 11A (sheet 2 of 2)

```
   1  gtaatcaaat tgtaaaggaa aaatattaat agtcagagta cacataaatg
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 101  gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg
 151  gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
 201  aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
 251  tatggctaat gttcccgacg agcacacacc gatgatgtca ccagtgaata
 301  caactacaaa gattctacaa cggagtggta ttaaaatgga aatcccgcca
 351  tatttggatc cagacagtca ggatgatgac ccggaagatg gtgtcaacta
 401  cccggatcca gatttatttg acacaaaaaa cacaaatatg accgagtacg
 451  atttggatgt gttgaagctt ggaaaaccag cagtagatga agcacggaaa
 501  aagatcgaag ttcccgacgc tagtgcgccg ccaaacaaaa ttgtagaata
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1251  tacccgttga acatgaaccc aattccgcaa atgccgcaaa tgccacaaat
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1351  cagaaaacaa caatccattc caccaaaatc accattataa tgatattagc
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1901  tttgaacgaa aaatggggaa caattgtgta ctatgagaaa aatttgcaaa
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```

Fig. 11B (sheet 1 of 2)

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2251  gcttcaacgt ttccaaacaa atcatcagag acgcgcttct ttccaagcaa
2301  atggcaacaa tgtacttgca aggaaaattg actccgatga attatatcta
2351  cgagaagaag actcaggaag agctgcgaag ggaagcaaca cgcaccactg
2401  attcattggc caagtactgt tgtgtccgtg tctcgttctg caaaggattt
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2501  tgagttgaaa atcaacattg cctacgattt catggattca atctgccagt
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2801  gttcattgtg agctttgagc tgtatagaag gacaatgtat cccatacctc
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2901  catatgtcat atattgcacc gtggcccttt ttattgtaac ttttaatata
2951  ttttcttccc aacttgtgaa tatgattgat gaaccaccat tttgagtaat
3001  aaatgtattt tttgtgg
```

Fig. 11B (sheet 2 of 2)

```
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 101  gttcaactat tctcagcccg gtaccagcac cggaggcccg ctttatggtg
 151  gaaaaccttc tcatggattg gaagatattc ctgatgtaga ggaatatgag
 201  aggaacctgc tcggggctgg agcaggtttt aatctgctca atgtaggaaa
 251  tatggctaat gaatttaaac caataatcac attggacacg aaaccacctc
 301  gtgatgccaa caagtcattg gcattcaatg gcgggttgaa gctaatcact
 351  ccgaaaactg aagttcccga cgagcacaca ccgatgatgt caccagtgaa
 401  tacaactaca aagattctac aacggagtgg tattaaaatg gaaatcccgc
 451  catatttgga tccagacagt caggatgatg acccggaaga tggtgtcaac
 501  tacccggatc cagatttatt tgacacaaaa aacacaaata tgaccgagta
 551  cgatttggat gtgttgaagc ttggaaaacc agcagtagat gaagcacgga
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 651  tatttgatgt attatagaac gttaaaagaa agtgaactca tacaactgaa
 701  tgcgtatcgg acaaaacgaa atcgattatc gttgaacttg gtcaaaaaca
 751  atattgatcg agagttcgac caaaaagctt gcgagtccct ggtgaaaaaa
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2051  aattggcgag aaaaaatgtt cgagaggaaa tttccacgtg gatggcggat
```

Fig. 11C (sheet 1 of 2)

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2201 cttttcctac aaaaaagacg ggagtgtttg gcttcaaaac cgcatgaagt
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2501 tgattcattg gccaagtact gttgtgtccg tgtctcgttc tgcaaaggat
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2601 attgagttga aaatcaacat tgcctacgat ttcatggatt caatctgcca
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3001 cgcatatgtc atatattgca ccgtggccct ttttattgta acttttaata
3051 tattttcttc ccaacttgtg aatatgattg atgaaccacc attttgagta
3101 ataaatgtat tttttgtgg

Fig. 11C (sheet 2 of 2)

```
  1  MKLIATSLLV PDEHTPMMSP VNTTTKILQR SGIKMEIPPY LDPDSQDDDP
 51  EDGVNYPDPD LFDTKNTNMT EYDLDVLKLG KPAVDEARKK IEVPDASAPP
101  NKIVEYLMYY RTLKESELIQ LNAYRTKRNR LSLNLVKNNI DREFDQKACE
151  SLVKKLKDKK NDLQNLIDVV LSKGTKYTGC ITIPRTLDGR LQVHGRKGFP
201  HVVYGKLWRF NEMTKNETRH VDHCKHAFEM KSDMVCVNPY HYEIVIGTMI
251  VGQRDHDNRD MPPPHQRYHT PGRQDPVDDM SRFIPPASIR PPPMNMHTRP
301  QPMPQQLPSV GATFAHPLPH QAPHNPGVSH PYSIAPQTHY PLNMNPIPQM
351  PQMPQMPPPL HQGYGMNGPS CSSENNNPFH QNHHYNDISH PNHYSYDCGP
401  NLYGFPTPYP DFHHPFNQQP HQPPQLSQNH TSQQGSHQPG HQGQVPNDPP
451  ISRPVLQPST VTLDVFRRYC RQTFGNRFFE GESEQSGAII RSSNKFIEEF
501  DSPICGVTVV RPRMTDGEVL ENIMPEDAPY HDICKFILRL TSESVTFSGE
551  GPEVSDLNEK WGTIVYYEKN LQIGEKKCSR GNFHVDGGFI CSENRYSLGL
601  EPNPIREPVA FKVRKAIVDG IRFSYKKDGS VWLQNRMKYP VFVTSGYLDE
651  QSGGLKKDKV HKVYGCASIK TFGFNVSKQI IRDALLSKQM ATMYLQGKLT
701  PMNYIYEKKT QEELRREATR TTDSLAKYCC VRVSFCKGFG EAYPERPSIH
751  DCPVWIELKI NIAYDFMDSI CQYITNCFEP LGMEDFAKLG INVSDD
```

Fig. 12A

```
  1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
 51 ERNLLGAGAG FNLLNVGNMA NVPDEHTPMM SPVNTTTKIL QRSGIKMEIP
101 PYLDPDSQDD DPEDGVNYPD PDLFDTKNTN MTEYDLDVLK LGKPAVDEAR
151 KKIEVPDASA PPNKIVEYLM YYRTLKESEL IQLNAYRTKR NRLSLNLVKN
201 NIDREFDQKA CESLVKKLKD KKNDLQNLID VVLSKGTKYT GCITIPRTLD
251 GRLQVHGRKG FPHVVYGKLW RFNEMTKNET RHVDHCKHAF EMKSDMVCVN
301 PYHYEIVIGT MIVGQRDHDN RDMPPPHQRY HTPGRQDPVD DMSRFIPPAS
351 IRPPPMNMHT RPQPMPQQLP SVGATFAHPL PHQAPHNPGV SHPYSIAPQT
401 HYPLNMNPIP QMPQMPQMPP PLHQGYGMNG PSCSSENNNP FHQNHHYNDI
451 SHPNHYSYDC GPNLYGFPTP YPDFHHPFNQ QPHQPPQLSQ NHTSQQGSHQ
501 PGHQGQVPND PPISRPVLQP STVTLDVFRR YCRQTFGNRF FEGESEQSGA
551 IIRSSNKFIE EFDSPICGVT VVRPRMTDGE VLENIMPEDA PYHDICKFIL
601 RLTSESVTFS GEGPEVSDLN EKWGTIVYYE KNLQIGEKKC SRGNFHVDGG
651 FICSENRYSL GLEPNPIREP VAFKVRKAIV DGIRFSYKKD GSVWLQNRMK
701 YPVFVTSGYL DEQSGGLKKD KVHKVYGCAS IKTFGFNVSK QIIRDALLSK
751 QMATMYLQGK LTPMNYIYEK KTQEELRREA TRTTDSLAKY CCVRVSFCKG
801 FGEAYPERPS IHDCPVWIEL KINIAYDFMD SICQYITNCF EPLGMEDFAK
851 LGINVSDD
```

Fig. 12B

1 MGDHHNLTGL PGTSIPPQFN YSQPGTSTGG PLYGGKPSHG LEDIPDVEEY
51 ERNLLGAGAG FNLLNVGNMA NEFKPIITLD TKPPRDANKS LAFNGGLKLI
101 TPKTEVPDEH TPMMSPVNTT TKILQRSGIK MEIPPYLDPD SQDDDPEDGV
151 NYPDPDLFDT KNTNMTEYDL DVLKLGKPAV DEARKKIEVP DASAPPNKIV
201 EYLMYYRTLK ESELIQLNAY RTKRNRLSLN LVKNNIDREF DQKACESLVK
251 KLKDKKNDLQ NLIDVVLSKG TKYTGCITIP RTLDGRLQVH GRKGFPHVVY
301 GKLWRFNEMT KNETRHVDHC KHAFEMKSDM VCVNPYHYEI VIGTMIVGQR
351 DHDNRDMPPP HQRYHTPGRQ DPVDDMSRFI PPASIRPPPM NMHTRPQPMP
401 QQLPSVGATF AHPLPHQAPH NPGVSHPYSI APQTHYPLNM NPIPQMPQMP
451 QMPPPLHQGY GMNGPSCSSE NNNPFHQNHH YNDISHPNHY SYDCGPNLYG
501 FPTPYPDFHH PFNQQPHQPP QLSQNHTSQQ GSHQPGHQGQ VPNDPPISRP
551 VLQPSTVTLD VFRRYCRQTF GNRFFEGESE QSGAIIRSSN KFIEEFDSPI
601 CGVTVVRPRM TDGEVLENIM PEDAPYHDIC KFILRLTSES VTFSGEGPEV
651 SDLNEKWGTI VYYEKNLQIG EKKCSRGNFH VDGGFICSEN RYSLGLEPNP
701 IREPVAFKVR KAIVDGIRFS YKKDGSVWLQ NRMKYPVFVT SGYLDEQSGG
751 LKKDKVHKVY GCASIKTFGF NVSKQIIRDA LLSKQMATMY LQGKLTPMNY
801 IYEKKTQEEL RREATRTTDS LAKYCCVRVS FCKGFGEAYP ERPSIHDCPV
851 WIELKINIAY DFMDSICQYI TNCFEPLGME DFAKLGINVS DD

Fig. 12C

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Fig. 13A

ttacacgtggccaatgcaacaatacatctatcaggaatcgtcagcaaccattccccatcaccatttaaatcaacacaaca
atccgtatcatccaatgcatcctcatcatcaattacctcatatgcaacaacttcctcaacctctattgaatcttaacatg
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Fig. 13B

MMEMLVDQGTDASSSASTSTSSVSRFGADTFMNTPDDVMMNDDMEPIPRDR
CNTWPMRRPQLEPPLNSSPIIHEQIPEEDADLYGSNEQCGQLGGASSNGST
AMLHTPDGSNSHQTSFPSDFRMSESPDDTVSGKKTTTRRNAWGNMSYAELI
TTAIMASPEKRLTLAQVYEWMVQNVPYFRDKGDSNSSAGWKNSIRHNLSLH
SRFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSR
RGAKKRIKERALMGSLHSTLNGNSIAGSIQTISHDLYDDDSMQGAFDNVPS
SFRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDR
TDQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLL
RNPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVA
AQHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL

Fig. 14A

MQQYIYQESSATIPHHHLNQHNNPYHPMHPHHQLPHMQQLPQPLLNLNMTT
LTSSGSSVASSIGGGAQCSPCASGSSTAATNSSQQQQTVGQMLAASVPCSS
SGMTLGMSLNLSQGGGPMPAKKKRCRKKPTDQLAQKKPNPWGEESYSDIIA
KALESAPDGRLKLNEIYQWFSDNIPYFGERSSPEEAAGWKNSIRHNLSLHS
RFMRIQNEGAGKSSWWVINPDAKPGMNPRRTRERSNTIETTTKAQLEKSRR
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FRPRTQSNLSIPGSSSRVSPAIGSDIYDDLEFPSWVGESVPAIPSDIVDRT
DQMRIDATTHIGGVQIKQESKPIKTEPIAPPPSYHELNSVRGSCAQNPLLR
NPIVPSTNFKPMPLPGAYGNYQNGGITPINWLSTSNSSPLPGIQSCGIVAA
QHTVASSSALPIDLENLTLPDQPLMDTMDVDALIRHELSQAGGQHIHFDL

Fig. 14B

```
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  61 cagatgcatg ttaacatttt acatccacaa ctgcaaacga tggtcgagca gtggcaaatg
 121 cgagaacgcc catcgctgga gaccgagaat ggcaaaggat cgctgctcct ggaaaatgaa
 181 ggtgtcgcag atatcatcac tatgtgtcca ttcggagaag ttattagtgt agtatttccg
 241 tggtttcttg caaatgtgcg aacatcgcta gaaatcaagc tatcagattt caaacatcaa
 301 cttttcgaat tgattgctcc gatgaagtgg ggaacatatt ccgtaaagcc acaggattat
 361 gtgttcagac agttgaataa tttcggcgaa attgaagtta tatttaacga cgatcaaccc
 421 ctgtcgaaat tagagctcca cggcactttc ccaatgcttt ttctctacca acctgatgga
 481 ataaacaggg ataaagaatt aatgagtgat ataagtcatt gtctaggata ctcactggat
 541 aaactggaag agagcctcga tgaggaactc cgtcaatttc gtgcttctct ctgggctcgt
 601 acgaagaaaa cgtgcttgac acgtggactt gagggtacca gtcactacgc gttccccgaa
 661 gaacagtact tgtgtgttgg tgaatcgtgc ccgaaagatt tggaatcaaa agtcaaggct
 721 gccaagctga gttatcagat gttttggaga aaacgtaaag cggaaatcaa tggagtttgc
 781 gagaaaatga tgaagattca aattgaattc aatccgaacg aaactccgaa atctctgctt
 841 cacacgtttc tctacgaaat gcgaaaattg gatgtatacg ataccgatga tcctgcagat
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 961 cttacgtctt atgatggtgt ccgttcggaa ctggaaagct atcgatgccc tggattcgtt
1021 gttcgccgac aatcactagt cctcaaagac tattgtcgcc caaaaccact ctacgaacca
1081 cattatgtga gagcacacga acgaaaactt gctctagacg tgctcagcgt gtctatagat
1141 agcacaccaa aacagagcaa gaacagtgac atggttatga ctgattttcg tccgacagct
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1381 aaatggaata aggaaatgta cacttttgat ctatacatga aggatatgcc accatctgca
1441 gtactcagca ttcgtgtttt gtacggaaaa gtgaaattaa aaagtgaaga attcgaagtt
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1561 ttccatctgt gggctcctga accgactgcc aatcgtagta ggatcggaga aaatggagca
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1741 ttgaatatta tgggtgatga ctatgagtcg tgtatcagag atccaggata taagaagctt
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1921 gaactcgcat ttgtgtggac tgatcgtgag aacttttccg agctctatgt gatgcttgaa
1981 aaatggaaac cgccgagtgt ggcagccgcg ttgactttgc ttggaaaacg ttgcacggat
2041 cgtgtgattc gaaagtttgc agtggagaag ttgaatgagc agctgagccc ggtcacattc
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2341 atcacccgac aagttgacat ggttgatgag ctcacacgaa tcagcactct tgtcaaagga
2401 atgccaaaag atgttgctac gatgaaactg cgtgacgagc ttcgatcgat tagtcataaa
2461 atggaaaata tggattctcc actggatcct gtgtacaaac tgggtgaaat gataatcgac
2521 aaagccatcg tcctaggaag tgcaaaacgt ccgttaatgc ttcactggaa gaacaaaaat
2581 ccaaagagtg acctgcacct tccgttctgt gcaatgatct tcaagaatgg agacgatctt
2641 cgccaggaca tgcttgttct tcaagttctc gaagttatgg ataacatctg gaaggctgca
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Fig. 15 (sheet 1 of 2)

2701 aacattgatt gctgtttgaa cccgtacgca gttcttccaa tgggagaaat gattggaatt
2761 attgaagttg tgcctaattg taaaacaata ttcgagattc aagttggaac aggattcatg
2821 aatacagcag ttcggagtat tgatccttcg tttatgaata agtggattcg gaaacaatgc
2881 ggaattgaag atgaaaagaa gaaaagcaaa aaggactcta cgaaaaatcc catcgaaaag
2941 aagattgata atactcaagc catgaagaaa tattttgaaa gtgtcgatcg attcctatac
3001 tcgtgtgttg gatattcagt tgccacgtac ataatgggaa tcaaggatcg tcacagtgat
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3181 tttatgacag tgattcgatc gggtaaatct gtggatggaa attcgcatga gctacaaaaa
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3361 gatcatttga agaaaaccct cttctgcaat ggagaaagca aagaagaagc gagaaagttt
3421 ttcgctggaa tctacgaaga agccttcaat ggatcatggt ctaccaaaac gaattggctc
3481 ttccacgcag tcaaacacta ctga

Fig. 15 (sheet 2 of 2)

```
   1 RKPWSSRSDC WTRTELRRIS QMHVNILHPQ LQTMVEQWQM RERPSLETEN GKGSLLLENE
  61 GVADIITMCP FGEVISVVFP WFLANVRTSL EIKLSDFKHQ LFELIAPMKW GTYSVKPQDY
 121 VFRQLNNFGE IEVIFNDDQP LSKLELHGTF PMLFLYQPDG INRDKELMSD ISHCLGYSLD
 181 KLEESLDEEL RQFRASLWAR TKKTCLTRGL EGTSHYAFPE EQYLCVGESC PKDLESKVKA
 241 AKLSYQMFWR KRKAEINGVC EKMMKIQIEF NPNETPKSLL HTFLYEMRKL DVYDTDDPAD
 301 EGWFLQLAGR TTFVTNPDVK LTSYDGVRSE LESYRCPGFV VRRQSLVLKD YCRPKPLYEP
 361 HYVRAHERKL ALDVLSVSID STPKQSKNSD MVMTDFRPTA SLKQVSLWDL DANLMIRPVN
 421 ISGFDFPADV DMYVRIEFSV YVGTLTLASK STTKVNAQFA KWNKEMYTFD LYMKDMPPSA
 481 VLSIRVLYGK VKLKSEEFEV GWVNMSLTDW RDELRQGQFL FHLWAPEPTA NRSRIGENGA
 541 RIGTNAAVTI EISSYGGRVR MPSQGQYTYL VKHRSTWTET LNIMGDDYES CIRDPGYKKL
 601 QMLVKKHESG IVLEEDEQRH VWMWRRYIQK QEPDLLIVLS ELAFVWTDRE NFSELYVMLE
 661 KWKPPSVAAA LTLLGKRCTD RVIRKFAVEK LNEQLSPVTF HLFILPLIQA LKYEPRAQSE
 721 VGMMLLTRAL CDYRIGHRLF WLLRAEIARL RDCDLKSEEY RRISLLMEAY LRGNEEHIKI
 781 ITRQVDMVDE LTRISTLVKG MPKDVATMKL RDELRSISHK MENMDSPLDP VYKLGEMIID
 841 KAIVLGSAKR PLMLHWKNKN PKSDLHLPFC AMIFKNGDDL RQDMLVLQVL EVMDNIWKAA
 901 NIDCCLNPYA VLPMGEMIGI IEVVPNCKTI FEIQVGTGFM NTAVRSIDPS FMNKWIRKQC
 961 GIEDEKKKSK KDSTKNPIEK KIDNTQAMKK YFESVDRFLY SCVGYSVATY IMGIKDRHSD
1021 NLMLTEDGKY VHIDFGHILG HGKTKLGIQR DRQPFILTEH FMTVIRSGKS VDGNSHELQK
1081 FKTLCVEAYE VMWNNRDLFV SLFTLMLGME LPELSTKADL DHLKKTLFCN GESKEEARKF
1141 FAGIYEEAFN GSWSTKTNWL FHAVKHY
```

Fig. 16

CONVERGENT TGF-β AND INSULIN SIGNALING ACTIVATE GLUCOSE-BASED METABOLISM GENES

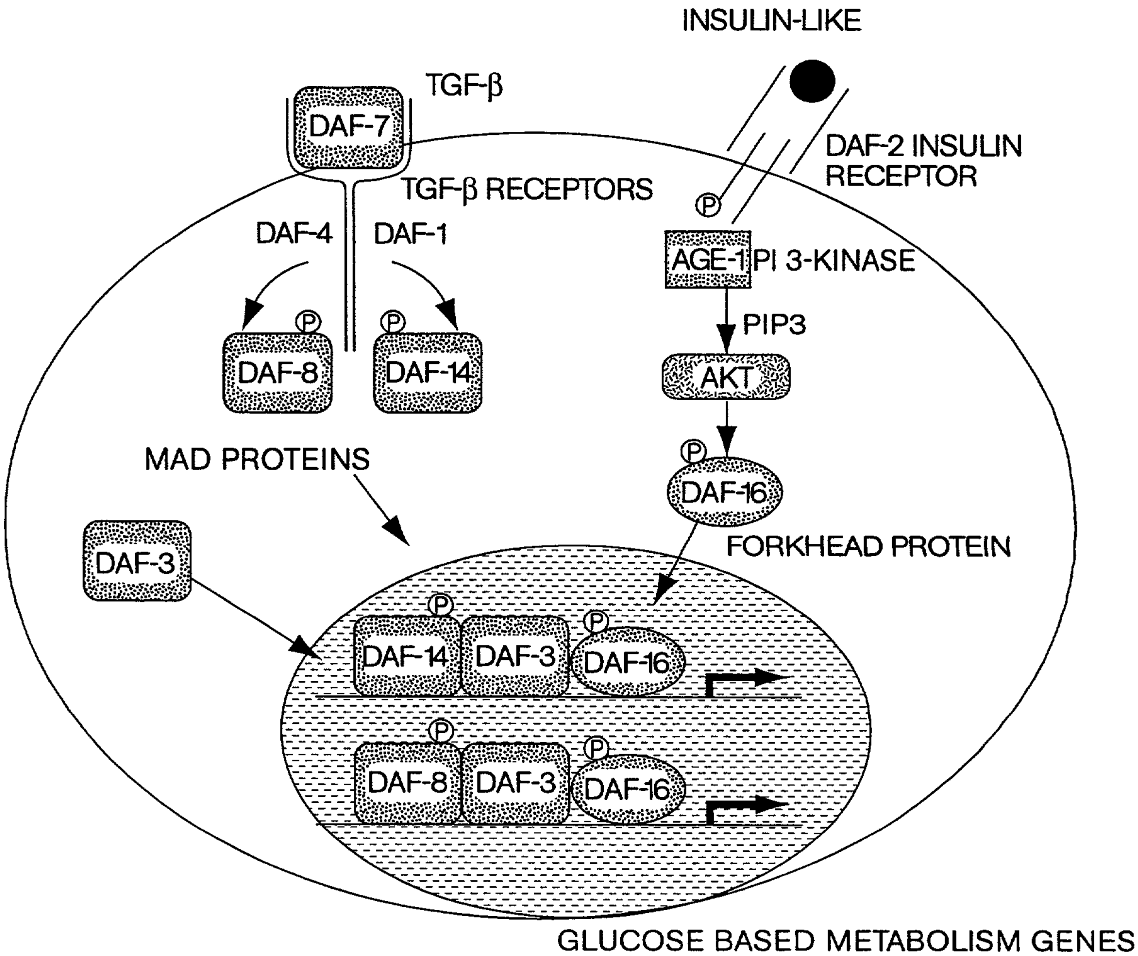
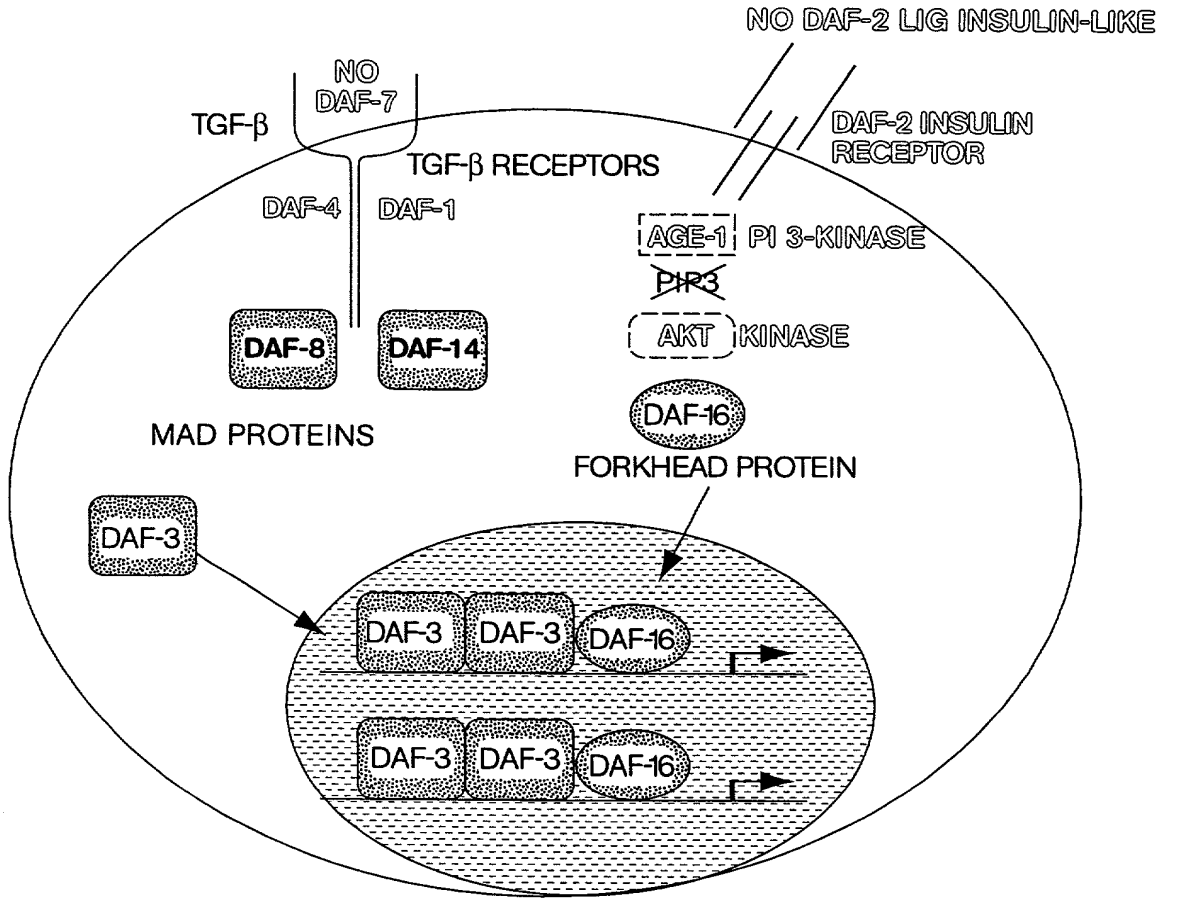


Fig. 17

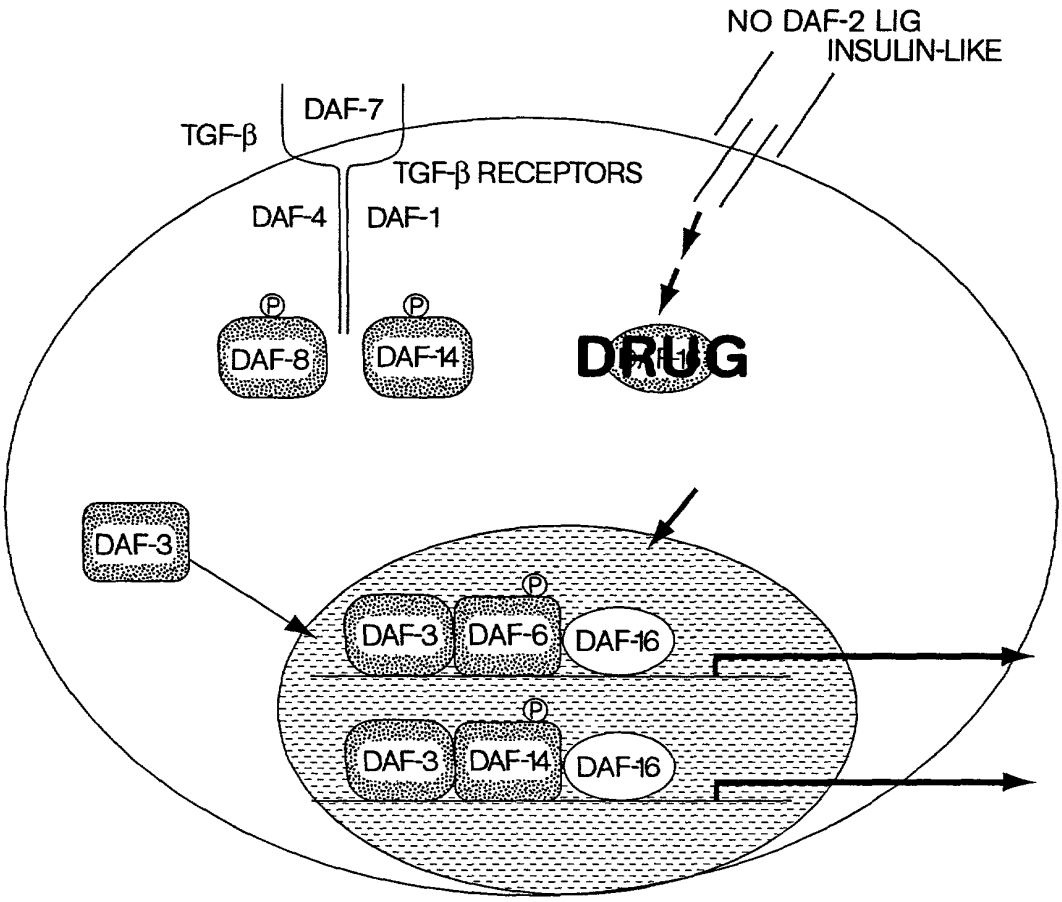
IN PHEROMONE, NO TGFβ OR INSULIN-LIKE SIGNALS CAUSES REPRESSION OF ANABOLIC GENES



REPRESS GLUCOSE BASED METABOLISM GENES
ACTIVE FAT METABOLISM

Fig. 18

**DRUGS THAT INHIBIT DAF-16 OR DAF-3
(OR PROTEINS IN THE PATHWAY)
CAN BE DISCOVERED USING REPORTER GENES
BEARING THEIR COGNATE BINDING SITES**



DRUG CAUSES A DECREASE IN DAF-16 ACTIVITY, ACTIVATING
THE REPORTER GENE LIKE A DAF-16 MUTANT.
THIS BYPASSES THE NEED FOR INSULIN

Fig. 19

DRUGS THAT INHIBIT DAF-3 WILL CURE THE DIABETES CAUSED BY A LACK OF DAF-7

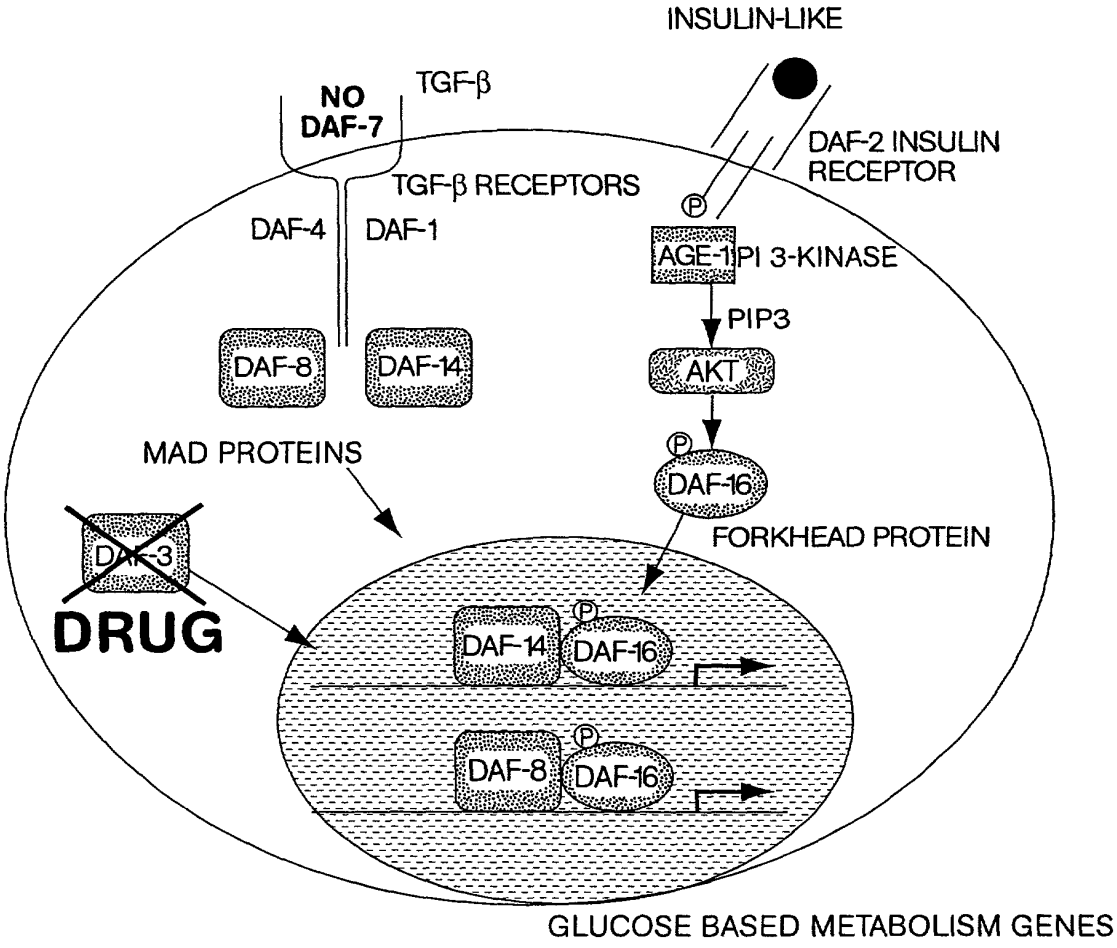


Fig. 20

```
             Hnf3a  .......... .......... .......... .......... .......... .....   0
             Hnf3g  .......... .......... .......... .......... .......... .....   0
D16123a467891011  MMEMLVDQGT DASSSASTST SSVSRFGADT FMNTPDDVMM NDDMEPIPRD RCNTW  55
 D1612567891011  MMEMLVDQGT DASSSASTST SSVSRFGADT FMNTPDDVMM NDDMEPIPRD RCNTW  55
               Afx  .......... .......... ......MRIQ PQKAAAIIDL DPDFEPQSRP RSCTW  29
              Fkhr  .......... .......... .......... MAEAPQVVEI DPDFEPLPRP RSCTW  25
         Consensus  ---------- ---------- ---------- ---------- --D-EP--R- R--TW  55

             Hnf3a  .......... ......MLGT VKMEGHETSD WNSYYADTQE AYSSVPVSNM NSGLG  39
             Hnf3g  .......... ......MLGS VKMEAHDLAE W.SYYPEAGE VYSPV..... .TPVP  32
D16123a467891011  PMRRPQLEPP LNSSPIIHEQ IPEEDADLYG SNEQCGQLGG ASSNGSTAML HTPDG 110
 D1612567891011  PMRRPQLEPP LNSSPIIHEQ IPEEDADLYG SNEQCGQLGG ASSNGSTAML HTPDG 110
               Afx  PLPRPEI... .......... .......... AN........ QPSEPPEVEP DLGEK  53
              Fkhr  PLPRPEF... .......... .......... SQSNSATSSP APSGSAAANP DAAAG  57
         Consensus  P--RP----- ---------- ---E------ -N-------- A-S------- ----G 110

             Hnf3a  SMNSMNTYMT MNTMTTSGNM TPASFNMSYA NPALGAGLSP .......... .....  79
             Hnf3g  TMAPLNSYMT LNPLSSP... YPGGLP...A SPLPSGPLAP .......... .....  66
D16123a467891011  SNSHQTSFPS D......... .......... .......... .......... ..... 121
 D1612567891011  SNSHQTSFPS ECYTWPMQQY IYQESSATIP HHHLNQHNNP YHPMHPHHQL PHMQQ 165
               Afx  VHT....... .......... .......... .......... .......... .....  56
              Fkhr  LPSASAAAVS ADFMS..... .......... .......... .......... .....  72
         Consensus  ---------- ---------- ---------- ---------- ---------- ----- 165

             Hnf3a  .........G AVAGMPGGSA GAMNSMTAAG VTAMGTALSP SGMGAMGAQQ AASMM 125
             Hnf3g  .........P APAAPLGPTF PGL....... ..GLSGGSSS SGYGAPGP.. .....  96
D16123a467891011  .......... .......... .......... .......... .......... ..... 121
 D1612567891011  LPQPLLNLNM TTLTSSGSSV ASSIGGGAQC SPCASGSSTA ATNSSQQQQT VGQML 220
               Afx  .......... .......... .......... .......... ......EGRS EPILL  65
              Fkhr  ........NL SLLEESEDFP QAPGSVAAAV AAAAAAAATG GLCGDFQGPE AGCLH 119
         Consensus  ---------- ---------- ---------- ---------- ---------- ----- 220

             Hnf3a  NGLGPYAAAM NPCMSPMAYA PSNLGRSRAG GGGDAKTFKR SY...PHAKP PYSYI 177
             Hnf3g  .......... .......... .......... GLVHGKEMPK GYRAPAHAKP PYSYI 121
D16123a467891011  .......... ......FRMS ESPDDTVSGK K......... .TTTRRNAWG NMSYA 150
 D1612567891011  AASVPCSSSG MTLGMSLNLS QGGGPMPAKK KRCRKKPTDQ LAQKKPNPWG EESYS 275
               Afx  PSRLSEPAGG P...QPGILG AVTGP..... .RK....... .GGSRRNAWG NQSYA 103
              Fkhr  PAPPQPPPPG PVSQHPPVPP AAAGPLAGQP RKS....... .SSSRRNAWG NLSYA 166
         Consensus  ---------- ---------- ---------- ---------- ------NAWG --SY- 275
```

Fig. 21A (sheet 1 of 3)

```
                Hnf3a   SLITMAIQRA PSKMLTLSEI YQWIMDLFPY YRQNQQR...  ..WQNSIRHS LSFND 227
                Hnf3g   SLITMAIQQA PGKVLTLSEI YQWIMDLFPY YRDNQQR...  ..WQNSIRHS LSFND 171
D16123a467891011        ELITTAIMAS PEKRLTLAQV YEWMVQNVPY FRDKGDSNSS AGWKNSIRHN LSLHS 205
  D1612567891011        DIIAKALESA PDGRLKLNEI YQWFSDNIPY FGERSSPEEA AGWKNSIRHN LSLHS 330
             Afx        EFISQAIESA PEKRLTLAQI YEWMVRTVPY FKDKGDSNSS AGWKNSIRHN LSLHS 158
            Fkhr        DLITKAIESS AEKRLTLSQI YEWMVKSVPY FKDKGDSNSS AGWKNSIRHN LSLHS 221
       Consensus        -LIT-AI--A P-KRLTL--I Y-W-----PY F-D------- AGWKNSIRHN LSLHS 330

                Hnf3a   CFVKVARSPD KPGKGSYWTL HPDSG.....  ........NM FENGCYLRRQ KRFKC 269
                Hnf3g   CFVKVARSPD KPGKGSYWAL HPSSG.....  ........NM FENGCYLRRQ KRFKL 213
D16123a467891011        RFMRIQN..E GAGKSSWWVI NPD.AKPGMN PRRTRERSNT IETTTKAQLE KSRRG 257
  D1612567891011        RFMRIQN..E GAGKSSWWVI NPD.AKPGMN PRRTRERSNT IETTTKAQLE KSRRG 382
             Afx        KFIKVHN..E ATGKSSWWML NPEGGKSGKA PRR...RAAS MDSSSKLLRG RSKAP 208
            Fkhr        KFIRVQN..E GTGKSSWWML NPEGGKSGKS PRR...RAAS MDNNSKFAKS RSRAA 271
       Consensus        -F--V-N--E --GKSSWW-L NP--GK-G-- PRR---R-N- -E---K---- KS--- 385

                Hnf3a   EKQPGAG...  GGGGSGSGGS GAKGGPESRK DPSGASNPSA DSPLHRGVHG KTGQL 321
                Hnf3g   EEKVKKG...  GSGASTTRNG TGSAASTTTP AATVTSPP..  .......... ..... 248
D16123a467891011        AKKRIKERAL  MGSLHSTLNG NSIAGSIQTI SHDLYDDDSM QGAFDNVPSS FRPRT 312
  D1612567891011        AKKRIKERAL  MGSLHSTLNG NSIAGSIQTI SHDLYDDDSM QGAFDNVPSS FRPRT 437
             Afx        KKKP......  .SVLPAPPEG ATPTSPVGHF AKWSGSPCSR NREEADMWTT FRPRS 256
            Fkhr        KKKA......  .S.LQSGQEG AG.DSPGSQF SKWPASPGSH SNDDFDNWST FRPRT 317
       Consensus        -KK-------  ---L-----G ----------  -----S--S- ---------- FRPR- 440

                Hnf3a   EGAPAPGPAA  SPQTLDHSGA TATGGASELK TPASSTAPPI SSGPGALASV PASHP 376
                Hnf3g   .QPPPPAPEP  EAQGGEDVGA LDCGS.....  .PASSTP...  .......... ..... 278
D16123a467891011        QSNLS.....  ..........  ..........  IPGSS.SRVS PAIGS..... ..... 331
  D1612567891011        QSNLS.....  ..........  ..........  IPGSS.SRVS PAIGS..... ..... 456
             Afx        SSNASSVSTR  LSPLRPESEV LAEE......  IPASV.SSYA GGVPPTLN.. ..EGL 300
            Fkhr        SSNASTISGR  LSPIMTEQDD LGEGDVHSMV YPPSA.AKMA STLPSLSEIS NPENM 371
       Consensus        -SN-S-----  ----------  ----------  -P-SS----- ---------- ----- 495

                Hnf3a   AHGLAPHESQ  LHLKGDPHYS FNHPFSINNL MSS.SEQQHK LDFKAYEQAL QYSPY 430
                Hnf3g   ..YFTGLELP  GDLKLDAPYN FNHPFSINNL MSEQTPAPPK LD.......V GFGGY 324
D16123a467891011        .DIYDDLEF.  ..PSWVGESV PAIP......  ..........  .......... ..... 351
  D1612567891011        .DIYDDLEF.  ..PSWVGESV PAIP......  ..........  .......... ..... 476
             Afx        E.LLDGLNLT  SSHSLLSRSG LSG.......  ..........  FSLQHPGVTG PLHTY 337
            Fkhr        ENLLDNLNLL  SSPTSLTVST QSSPGTMMQQ TPCYSFAPPN TSLNSPSPNY QKYTY 426
       Consensus        ----D-LE--  --------S- ---P------ ----------  ---------- ----Y 550
```

Fig. 21A (sheet 2 of 3)

```
Hnf3a              GSTLPASLPL GSASVTTRSP IEPSALEPAY YQGVYSRPVL NTS....... ..... 473
Hnf3g              GAE....... .......... ...GGEPGVY YQGLYSRSLL NAS....... ..... 347
D16123a467891011   .....SDIVD RTDQMRIDAT THIGGVQ... .IKQESKPIK TEPIAPPPSY HELNS 397
D1612567891011     .....SDIVD RTDQMRIDAT THIGGVQ... .IKQESKPIK TEPIAPPPSY HELNS 522
Afx                SSSLFSP... ........AE GPLSAGEGCF SSSQALEALL TSDTPPPPAD VLMTQ 381
Fkhr               GQSSMSPLPQ MPIQTLQDNK SSYGGMSQYN CAPGLLKELL TSDSPPH..N DIMTP 479
Consensus          -----S---- ---------- ---GG----- -----S---L T----P---- ----- 605

Hnf3a              .......... .......... .......... .......... .......... ..... 473
Hnf3g              .......... .......... .......... .......... .......... ..... 347
D16123a467891011   VRGSCAQNP. .LLRNPIVPS TNFKPMPLPG AYGNYQNGGI TPINWLSTSN SSPLP 450
D1612567891011     VRGSCAQNP. .LLRNPIVPS TNFKPMPLPG AYGNYQNGGI TPINWLSTSN SSPLP 575
Afx                VDPILSQAPT LLL....... .......LGG LPSS..SKLA TGVGLC.... PKPLE 416
Fkhr               VDPGVAQPNS RVLGQNVMMG PNSVMSTYGS QASH..NKMM NPSSHTHPGH AQQTS 532
Consensus          V-----Q--- --L------- ---------- ---------- ---------- ----- 660

Hnf3a              .......... .......... .......... .......... .......... ..... 473
Hnf3g              .......... .......... .......... .......... .......... ..... 347
D16123a467891011   GIQSCGIVAA QHTVASSSAL PIDLENLTLP DQPLMDTM.. .......... ..... 488
D1612567891011     GIQSCGIVAA QHTVASSSAL PIDLENLTLP DQPLMDTM.. .......... ..... 613
Afx                ARGPSSLVPT LSMIAPPPVM AS........ .APIPKALGT PVLTPPTEAA S.... 458
Fkhr               AVNGRPLPHT VSTMPHTSGM NRLTQVKTPV QVPLPHPMQM SALGGYSSVS SCNGY 587
Consensus          ---------- ---------- ---------- --P------- ---------- ----- 715

Hnf3a              .......... .......... .......... .......... .......... ..... 473
Hnf3g              .......... .......... .......... .......... .......... ..... 347
D16123a467891011   .......... .......... ......DVDA LIRHELSQAG GQHIHFDL.. ..... 510
D1612567891011     .......... .......... ......DVDA LIRHELSQAG GQHIHFDL.. ..... 635
Afx                .......QDR MPQDLDLDMY MENLECDMDN IISDLMDEGE GLDFNFEPDP ..... 501
Fkhr               GRMGLLHQEK LPSDLD.GMF IERLDCDMES IIRNDLMDGD TLDFNFDNVL PNQSF 641
Consensus          ---------- ---------- ------D--- -I-------- -----F---- ----- 770

Hnf3a              .......... .... 473
Hnf3g              .......... .... 347
D16123a467891011   .......... .... 510
D1612567891011     .......... .... 635
Afx                .......... .... 501
Fkhr               PHSVKTTTHS WVSG 655
Consensus          ---------- ---- 784
```

Fig. 21A (sheet 3 of 3)

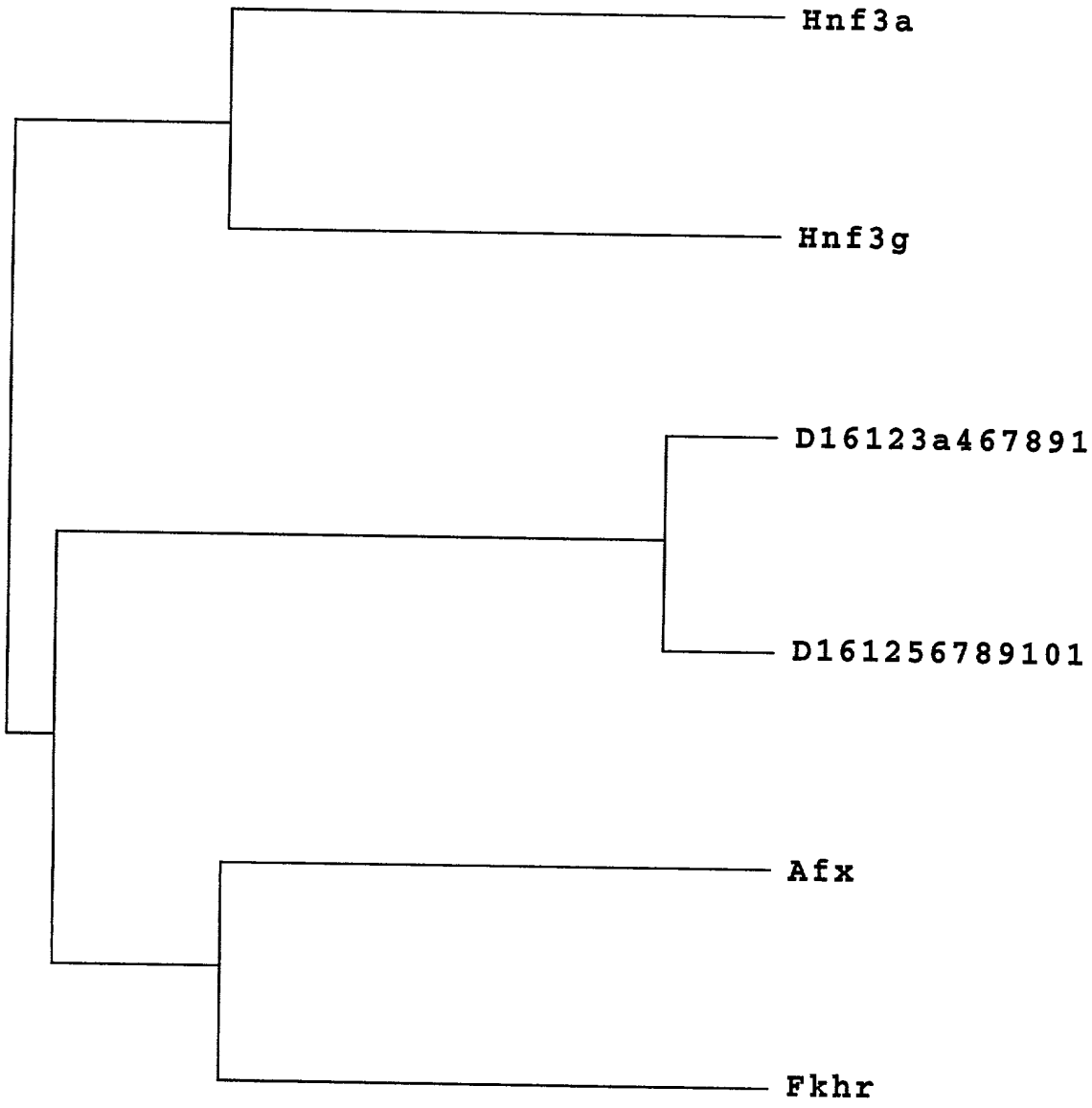


Fig. 21B

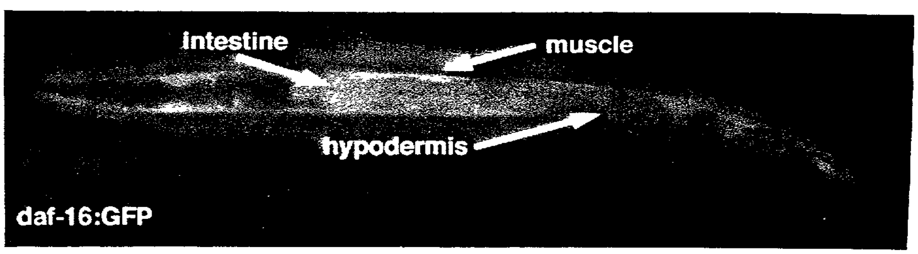
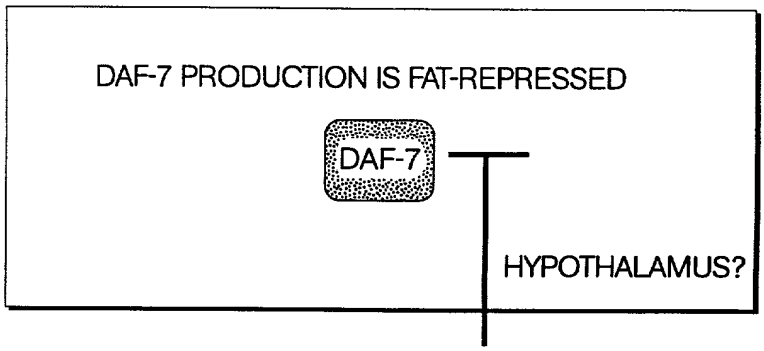


Fig. 22

INJECTION OF OF DAF-7 BYPASSES OBESITY-INDUCED DEFECTS IN INSULIN-REGULATION OF METABOLISM



FATTY ACIDS IN BLOOD REPRESS DAF-7 IN ANALOGY TO PHEROMONE REGULATION OF DAF-7 IN C. ELEGANS

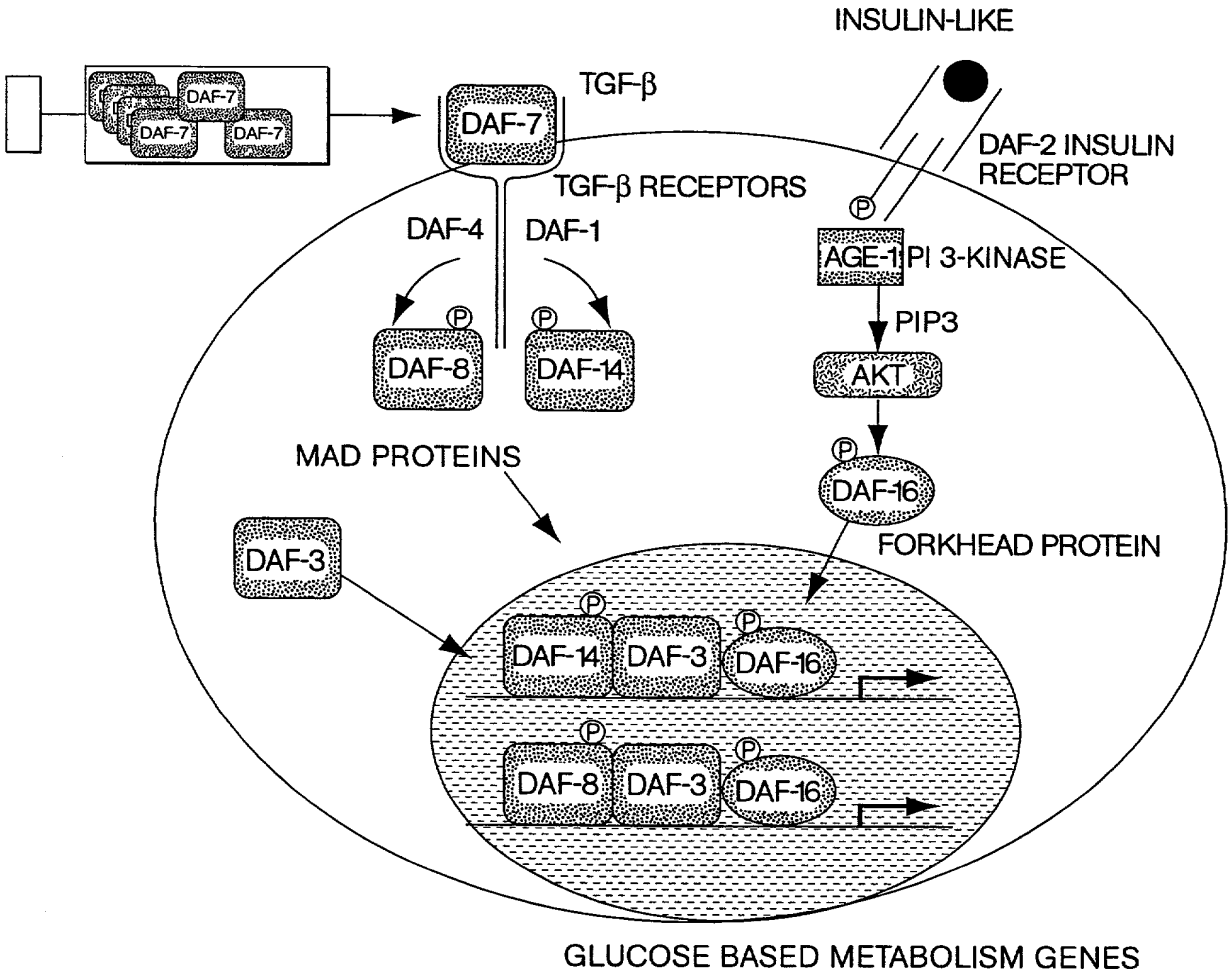


Fig. 23

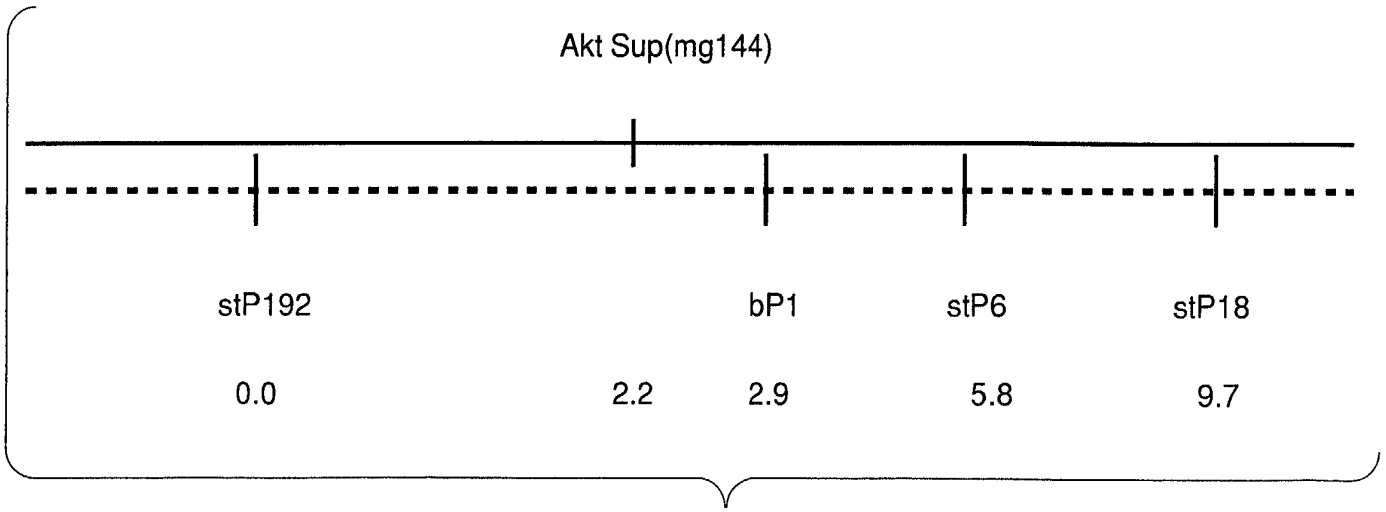


Fig. 24

Comparison of the human AKT protein sequence to the cosmid sequence C12D8, located in the genetic interval where sup(mg144) maps. Numbering in the AKT protein sequence by amino acid residues, and in the cosmid sequence by nucleotide position.

```
 Score = 450 (207.4 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 79/121 (65%), Positives = 97/121 (80%), Frame = +1

Query:    319 EVLEDNDYGRAVDWWGLGVVMYEMMCGRLPFYNQDHEKLFELILMEEIRFPRTLGPEAKS 378
              +VL+D+DYGR VDWWG+GVVMYEMMCGRLPFY++DH KLFELI+  ++RFP  L  EA++
Sbjct:  33685 QVLDDHDYGRCVDWWGVGVVMYEMMCGRLPFYSKDHNKLFELIMAGDLRFPSKLSQEART 33864

Query:    379 LLSGLLKKDPTQRLGGGSEDAKEIMQHRFFANIVWQDVYEKKLSPPFKPQVTSETDTRYFD 439
              LL+GLL KDPTQRLGGG EDA EI +  FF  + W+  Y K++ PP+KP V SETDT YFD
Sbjct:  33865 LLTGLLVKDPTQRLGGGPEDALEICRADFFRTVDWEATYRKEIEPPYKPNVQSETDTSYFD 34047

 Score = 256 (118.0 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 48/66 (72%), Positives = 59/66 (89%), Frame = +1

Query:    146 TMNEFEYLKLLGKGTFGKVILVKEKATGRYYAMKILKKEVIVAKDEVAHTLTENRVLQNS 205
              TM +F++LK+LGKGTFGKVIL KEK T + YA+KILKK+VI+A++EVAHTLTENRVLQ
Sbjct:  32314 TMEDFDFLKVLGKGTFGKVILCKEKRTQKLYAIKILKKDVIIAREEVAHTLTENRVLQRC 32493

Query:    206 RHPFLT 211
              +HPFLT
Sbjct:  32494 KHPFLT 32511

 Score = 190 (87.6 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 36/45 (80%), Positives = 37/45 (82%), Frame = +2

Query:    276 KLENLMLDKDGHIKITDFGLCKEGIKDGATMKTFCGTPEYLAPEV 320
              KLENL+LDKDGHIKI DFGLCKE I  G    TFCGTPEYLAPEV
Sbjct:  33509 KLENLLLDKDGHIKIADFGLCKEEISFGDKTSTFCGTPEYLAPEV 33643

 Score = 188 (86.7 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 37/57 (64%), Positives = 42/57 (73%), Frame = +3

Query:    209 FLTALKYSFQTHDRLCFVMEYANGGELFFHLSRERVFSEDRARFYGAEIVSALDYLH 265
              +   LKYSFQ    LCFVM++ANGGELF H+ +   FSE RARFYGAEIV AL YLH
Sbjct:  32667 YFQELKYSFQEQHYLCFVMQFANGGELFTHVRKCGTFSEPRARFYGAEIVLALGYLH 32837

 Score = 166 (76.5 bits), Expect = 5.2e-165, Sum P(7) = 5.2e-165
 Identities = 29/59 (49%), Positives = 42/59 (71%), Frame = +1

Query:     53 NNFSVAQCQLMKTERPRPNTFIIRCLQWTTVIERTFHVETPEEREEWATAIQTVADGLK 111
              + F++   Q M  E+PRPN F++RCLQWTTVIERTF+ E+ E R+ W  AI++++   K
Sbjct:  31846 STFAIFYFQTMLFEKPRPNMFMVRCLQWTTVIERTFYAESAEVRQRWIHAIESISKKYK 32022

 Score = 134 (61.8 bits), Expect = 5.2e-167, Sum P(8) = 5.2e-167
 Identities = 24/33 (72%), Positives = 30/33 (90%), Frame = +3

Query:    210 LTALKYSFQTHDRLCFVMEYANGGELFFHLSRE 242
              L  LKYSFQT+DRLCFVME+A GG+L++HL+RE
Sbjct:  33156 LQELKYSFQTNDRLCFVMEFAIGGDLYYHLNRE 33254
```

Fig. 25

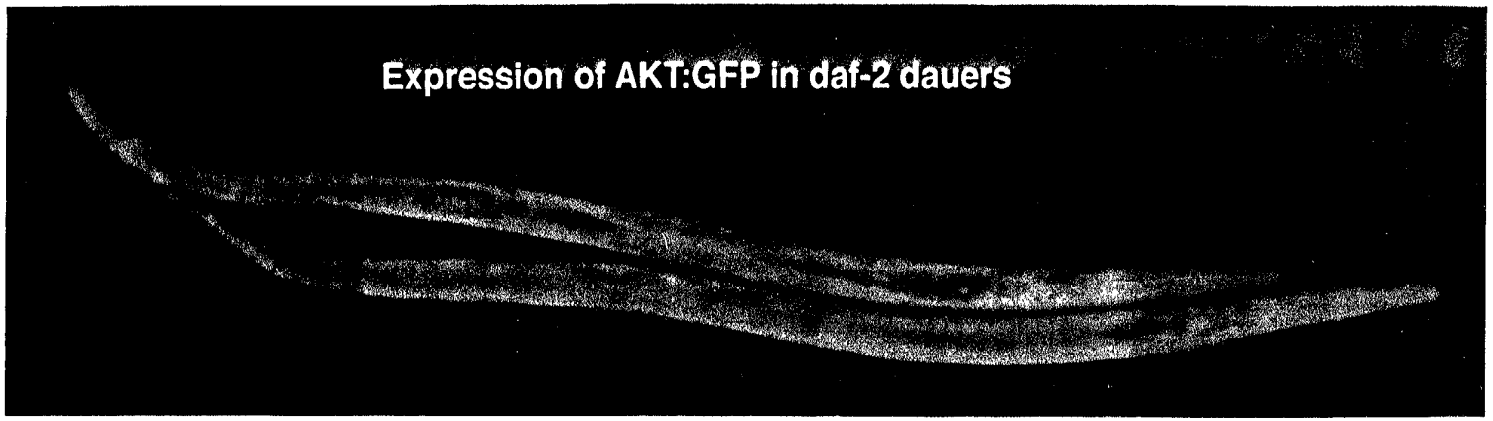


Fig. 26A

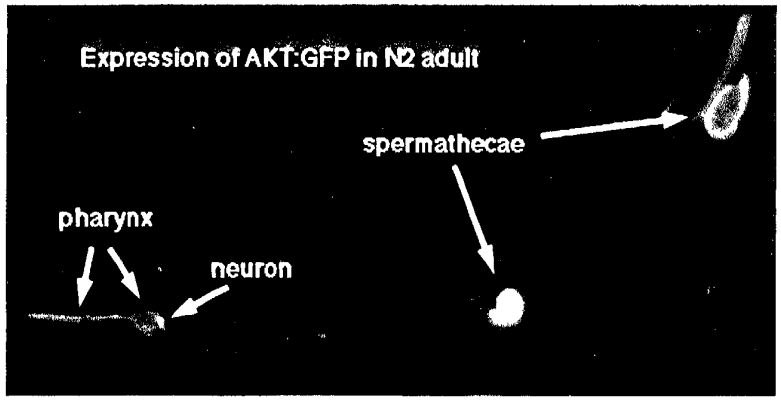


Fig. 26B

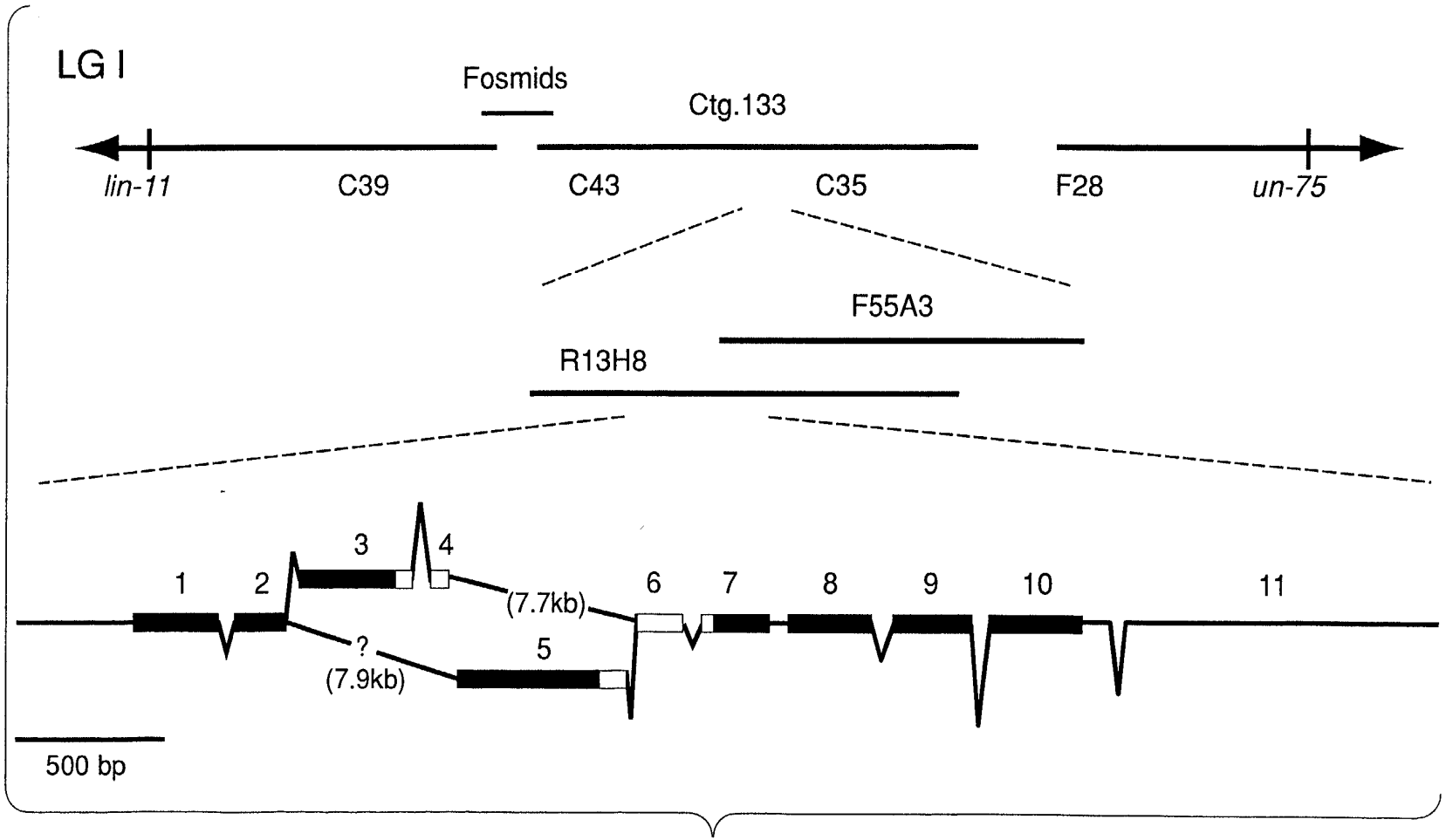


Fig. 27